

American Journal of
DIGESTIVE DISEASES
Volume 11

The American Journal of DIGESTIVE DISEASES

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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THE SUNSET YEARS AND

Adequate Nutrition

As the degenerative processes gain the upper hand during the last decade or two of life, profound changes occur in many metabolic mechanisms. The gastrointestinal tract for example becomes less tolerant of abuses, and difficulty is experienced in digesting some foods which formerly did not prove troublesome. The loss of vigor characteristic of senescence can easily be aggravated to a point of incapacitation if eating habits are not altered to prevent nutritional deficiencies. For only by properly satisfying the nutritional requirements can adequate strength be maintained.

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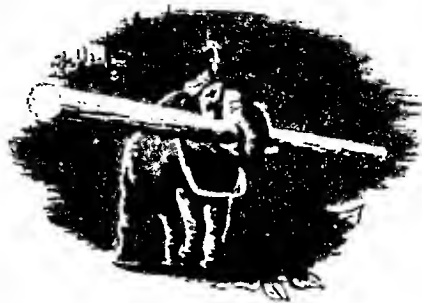
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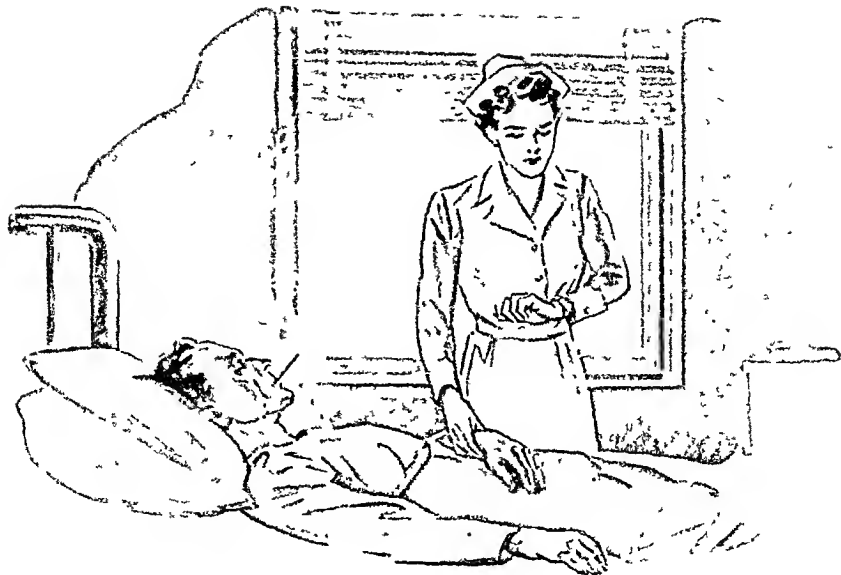
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In the Dietary Adjustment **DEMANDED BY FEBRILE DISEASE**

During periods of acute febrile disease, dietary adjustment must be made to satisfy the change in nutritional demands. Protein requirements are increased 50 to 100 per cent, caloric expenditure is raised because of increased heat loss, and vitamin needs, especially those of the water-soluble groups, are greater. Only by fully meeting these altered requirements can recovery be hastened, can convalescence be shortened, and the usual state of lethargy reduced in severity.

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RATIONING DOES NOT CHANGE *Nutritional Needs*

As food availability decreases through increased ration control, many persons may be required to make drastic dietary adjustments to maintain their former health and vigor. These changes will be especially demanded of workers in essential and other industries whose energy expenditure is greater today than ever before. Regardless of curtailed food supplies, nutritional needs remain unchanged, hence new means for their satisfaction must be employed.

Ovaltine provides an excellent answer to the problem of satisfying metabolic requirements in the face of more stringent rationing and food shortages. It provides the nutrients concerned with well-being and especially those whose lack is most likely to occur under food rationing. Three glassfuls of this delicious food drink may well raise the average diet to nutritional adequacy. Ovaltine is equally appealing as a meal-time beverage and as a between-meal snack.

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Vitamins Alone

MAY NOT BE ADEQUATE

The current popularization of the importance of vitamins, though true in most respects, may prove harmful because of the decreased emphasis placed upon other essential nutrients. A good nutritional state can be achieved only by satisfying all nutritional requirements, not merely vitamins, but minerals and proteins as well.

A food supplement in the literal sense of the word, Ovaltine is a balanced mixture of nutrients which provides virtually all metabolic essen-

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More than so-termed tonics and restoratives, Ovaltine can materially shorten the period required for the return of strength and vigor following recovery from infectious or prolonged illnesses. During the acute stages of febrile diseases, when the patient's nutritional intake is low, while requirements are higher than normal, many metabolic deficits are developed. These can be made good only by a high intake of essential nutrients during the recovery period, for only

after these nutritional deficits are wiped out can former strength and well-being return.

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PHOSPHORUS25 Gm.	.903 Gm.	NIACIN	3.0 mg.	5.0 mg.
IRON	10.5 mg.	11.91 mg.	COPPER5 mg.	.5 mg.

*Each serving made with 8 oz. of milk; based on average reported values for milk.

The American Journal of DIGESTIVE DISEASES

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CALCIUM25 Gm	1.104 Gm	RIBOFLAVIN25 mg	1.278 mg
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IRON	10.5 mg	11.94 mg	COPPER5 mg	5 mg

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A Review of Hypoglycemia, Its Physiology and Pathology, Symptomatology and Treatment

By

HAROLD E. HIMWICH, M.D.*

ALBANY, NEW YORK

CLINICALLY hypoglycemia presents itself both as a diagnostic and a therapeutic problem. Numerous studies both on humans and animals have afforded much new information on the role of carbohydrate in bodily functions as well as the reactions of the body, neurological and endocrinological to hypoglycemia. It is in the hope of correlating this newer knowledge with that which is already known that this review is written.

Hypoglycemia may arise in any physician's practice as a result of a number of causes. It may be contracted through diseases of the liver, one or another of the endocrine glands, or accidentally, through an overdosage of insulin and failure to ingest sufficient carbohydrate in the treatment of diabetes. Recently, it has been adopted by Sakel (1) as part of the treatment for schizophrenia. In the light of its frequent occurrence, a more complete understanding of the implications involved in hypoglycemic symptoms is in order. This is necessary not only for a differential diagnosis between hypoglycemic and diabetic coma, but also on the grounds that the symptoms of hypoglycemia are an index to the depth of the coma; for example, the ability to recognize the early symptoms permits the physician to forestall further progress of the condition and gives him the assurance that proper treatment will be followed by speedy recovery. Other symptoms which develop as the hypoglycemic progresses indicate a more profound depression which becomes increasingly difficult to relieve even though the physician has been successful in raising the blood sugar to normal or above. Considering the prognostic significance of the symptoms of hypoglycemia, there is added import to their study.

In order to understand the pathological changes resulting from a depletion of carbohydrate, one must be familiar with the physiological mechanisms which tend to regulate and maintain the constancy of the blood sugar.

THE PHYSIOLOGICAL CONTROL OF BLOOD SUGAR

Blood sugar is stabilized within narrow limits in the postabsorptive condition. Between 70 and 110 mgm. per cent is a normal concentration of blood sugar for a healthy individual before he has his breakfast. Though any value below 70 mgm. per cent may be considered abnormally low, we recognize hypoglycemia clinically only when blood sugar has fallen so low that signs and symptoms become conspicuous. It takes a blood sugar below 60 mgm. per cent before such symptoms become prominent.

Only under postabsorptive conditions is the level of blood sugar constant. During the day there are fairly wide shifts accompanying and following each meal. The level rises rapidly after each meal containing carbohydrate and falls thereafter. These prandial variations in blood sugar however are limited between certain extremes, beyond which it should be recognized as an abnormality and treated as such. After a meal, sugar rises to 180 mgm. per cent or less. The drop between meals may bring blood sugar levels even lower than the postabsorptive one in the morning. Here, the blood sugar is restored to normal by certain control mechanisms which, as we shall see, operate not only in hypoglycemic emergencies, but regulate the level of blood sugar at all times.

When it is understood within what narrow limits blood sugar is maintained, it is obvious that if hypoglycemia does supervene, these controlling mechanisms are no longer functioning adequately. Let us, then, briefly review the construction and operation of these mechanisms whose duty it is to keep our blood sugar within its normal ranges.

THE LIVER

Because carbohydrate is constantly utilized by the healthy body as a source of energy, it must be ingested if its metabolism is to continue. But the glucose of the blood does not arise only from the ingested carbohydrate. Both the amino acids derived from protein and the glycerol fraction of fat may also yield carbohydrate. The store house for carbohydrate is, as we already know, the liver, and this important organ is also the chief site of transformation of amino acids and glycerol to glycogen. Other important intermediary metabolites like lactic acid and pyruvic acid are also converted to glycogen in the liver. Glycogen is released from the liver into the blood stream for distribution between meals, and this may be said to be a most significant duty of the liver. The fact that hepatectomy is followed by fatal hypoglycemia proves the important contribution which the liver makes in controlling blood sugar content.

PARASYMPATHETIC-INSULIN SYSTEM

The level of blood sugar which is supported by ingested carbohydrate at meal times, and by hepatic glucose between meals, is under a complicated control which prevents any harmful rise or fall in the level. Only one element that we know of limits the rise of blood sugar, but there are several acting in different

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ways to prevent its fall, a much more serious disturbance. The only machinery preventing a rise in blood sugar is the para-sympathetic-insulin apparatus, which works in the following order: a high level of blood sugar provokes the secretion of insulin, partly as the result of a nervous reflex (2). This nervous response is initiated by the stimulating effect of hyperglycemia exerted upon the interacting para-sympathetic centers in the hypothalamus and the medulla oblongata. The vagus, arising from the medulla, then sends branches to the islands of Langerhans from which insulin is liberated. The islands of Langerhans also react directly to the raised level of blood sugar, that is, they may respond without mediation of the vagus, for insular activity is increased even though the pancreas may be denervated (3). Thus, we see that the nervous reflex is only of minor importance, but probably renders the secretory apparatus more sensitive to small variations of blood sugar by exerting a moderating and refining influence.

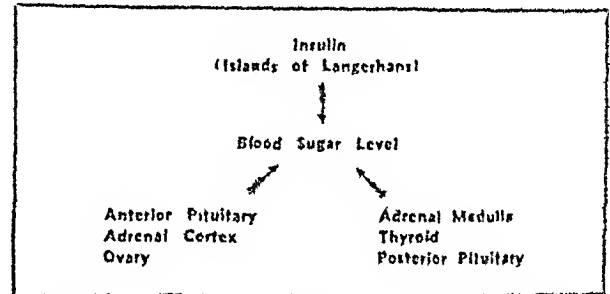
NEUROENDOCRINE DEFENSE AGAINST LOW BLOOD SUGAR

Perhaps the foremost antagonist to the para-sympathetic-insulin apparatus is the sympathetic-adrenalin system (4). Whenever blood sugar drops to dangerously low levels, whether by excessive insulin or for any other reason, the sympathetic-adrenalin equipment goes into increased activity. In response to a low blood sugar cerebral centers in the hypothalamus, pons and medulla send impulses down the cord to the lateral horns, impulses which then pass out from the cord and travel through the splanchnic nerves to the adrenal medulla to stimulate the secretion of adrenalin (5). This hormone mobilizes liver glycogen which is then released into the blood stream as glucose in large quantities to combat hypoglycemia. It is a fact that nervous mediation occupies a more important position in this chain of activity than it does in the para-sympathetic-insulin apparatus, the explanation being that the adrenal medulla is not directly sensitive, as are the islands of Langerhans, to the level of blood sugar. Section of the splanchnic nerves prevents almost completely the response of the sympathetic-adrenalin apparatus to low blood sugar.

The defense against the fall of blood sugar is a complicated one and includes much more than sympathetic-adrenalin apparatus, important as it is. Acting synergistically with the adrenal medulla are the thyroid (6) and posterior pituitary glands (7). All three glands accelerate the release of hepatic glucose into the blood stream and in this way sustain the level of the blood sugar. Two other endocrine glands—the anterior pituitary (8) and the adrenal cortex (9, 10, 11)—are also active in the endocrine balance working against hypoglycemia. These two glands raise blood sugar not by mobilizing liver glycogen, but by diminishing the oxidation of carbohydrate. The hormones of these two glands, therefore, are diabetogenic in character. Though the internal secretion of the ovary is also diabetogenic, it acts indirectly by stimulating the activities of the anterior pituitary and adrenal cortex (12). When the normal

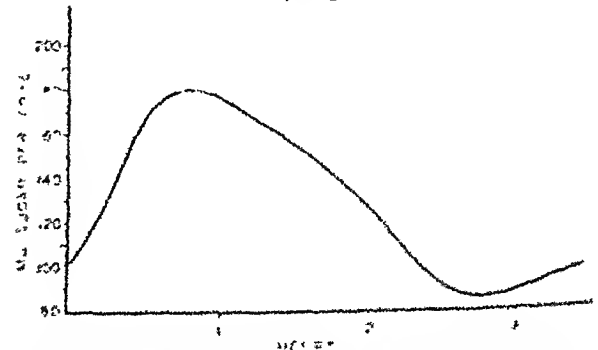
function of these two glands become excessive, diabetes will develop. This kind of diabetes is part of the syndrome of acromegaly (13), which disease results from adenoma of the anterior pituitary gland. A similar type of diabetes has been reported in patients with cortical adenoma (14, 15). In addition to depressing carbohydrate oxidation the adrenal cortex regulates blood sugar by another method. It accelerates the transformation of protein to carbohydrate in the liver. The anterior pituitary exerts the same effect indirectly through the activity of its corticotrophic hormone on the adrenal cortex. In general, we see that the hormones preventing hypoglycemia are divided into two groups: one which calls for more glucose from the liver and the other which diminishes carbohydrate oxidation and also increases the conversion of protein to carbohydrate. So dangerous is hypoglycemia to the organism that nature has provided this intricate and multiple defense to avert such a catastrophe. It might be diagrammed as follows:

FIGURE 1



The integrated action of all the factors which control the level of blood sugar is disclosed on an analysis of the glucose tolerance curve. Starting with a patient in the postabsorptive state whose only source of blood sugar is liver glycogen, we find that he is not subjected to hypoglycemia because his insulin apparatus is in abeyance and his anterior pituitary and adrenal cortical hormones are depressing the oxidation of glucose, thereby conserving his reserves of carbohydrate. After he

FIG. 2



GLUCOSE TOLERANCE CURVE:
Effect of administering 100 grams of glucose on the concentration of blood glucose of a normal subject in the postabsorptive state.

ingests the glucose of the test meal (1 to 2 gm. of glucose per kilo) it is quickly absorbed and reaches its maximum value in the blood in approximately 1 hour. This rise of blood sugar stimulates the para-sympathetic-insulin apparatus and under the influence of the

newly secreted insulin, the blood sugar is limited to 180 mgm. per cent. Other factors acting with insulin are the intrinsic function of the liver to absorb sugar and store it as glycogen, and the fact that diabetogenic activities of the anterior pituitary and adrenal cortex have been checked. This shift in the carbohydrate balance which makes for the increased utilization of blood sugar continues for some time after the absorption from the gastrointestinal tract has been completed and for this reason, blood sugar may decrease to low levels. If it falls below the postabsorptive level, the emergency mechanism, which goes into activity whenever hypoglycemia threatens, begins to function. The sympathetic-adrenalin apparatus is stimulated, adrenalin is liberated, hepatic glucose poured out, and blood sugar is brought back to the normal level. Finally the postabsorptive endocrine balance is re-established as insulin secretion ceases while that of the anterior pituitary and adrenal cortex again resume their diabetogenic activity.

THE FUNCTIONAL PATHOLOGY OF HYPOGLYCEMIA

Keeping the above review in mind, we may condense the causes which lower blood sugar into a tripartite classification: (a) hepatic failure, (b) excessive insulin, and (c) a defect in the endocrine defense against hypoglycemia.

FAILURE OF THE LIVER

Since it is one duty of the liver to release glucose continuously into the blood stream, it follows that failure of hepatic function should lead to hypoglycemia. Conn (16) reports a case of hepatogenic hypoglycemia in a laborer, aged 47, with periodic attacks of unconsciousness, occurring usually from 9 to 12 hours after his evening meal. The attacks were characterized by perspiration, drowsiness, and disorientation followed by unconsciousness with vomiting and incontinence of urine and feces. There were no convulsions. Feeding would end his attack almost at once and there was complete amnesia for the entire episode. The fasting level of blood sugar was low but the glucose tolerance test revealed a high delayed curve. Evidence of marked impairment of liver function was found in retention of bromsulphalein, diminished galactose tolerance, positive urinary urobilinogen test and abnormally low total serum proteins, with inversion of the albumin-globulin ratio. A cholecystogram showed visualization of the gall bladder with suspected stones. A cholecystectomy was, therefore, performed. During the operation the pancreas was examined carefully and found to be normal. The liver was of normal size but pale and granular, with surface nodules, about 2 mm. in diameter. The gall bladder was distended and contained several large stones and from 60 to 90 cc. of thick yellow pus. Biopsy of the liver showed active chronic cholangiolitis leading to early biliary cirrhosis. Normal function of the liver returned in the postabsorptive period. It was apparent that the pre-operative hypoglycemia and the delay of the glucose tolerance test was due to impaired ability of the liver to form glycogen.

Sometimes the liver is damaged so severely that the condition cannot be remedied and in such cases the patients die in hypoglycemia. This has been reported in patients with chloroform poisoning (17), or acute yellow atrophy of the liver (18). In the laboratory hepatic damage has been effected in chloroform (19), phosphorus, carbon tetrachloride (20) and guanidine poisoning, and by experimental yellow fever (21).

An infant is at a greater disadvantage than an adult when his carbohydrate supplies to the liver are curtailed, since he has not as yet attained any degree of stability in his neuroendocrine balance. His carbohydrate reserve may be dangerously lowered by starvation (22), vomiting, or diarrhea (23). In fact, hypoglycemia has frequently been reported in malnourished infants or in children subjected to recurrent vomiting. Severe diarrhea may be attended by low blood sugar as observed in infants with coeliac disease and in adults with sprue. Finally, in the relatively rare von Gierke's disease (24), hypoglycemia may occur despite ample hepatic glycogen stores. The infant with protruding abdomen caused chiefly by a massive liver, reveals a low fasting blood sugar. This disease must be caused by the failure of hepatic glycogen to break down to glucose (25). In all of these instances of hepatogenous hypoglycemia, blood sugar fell because the neuroendocrine balance was not given the necessary glucose to work upon.

EXCESSIVE INSULIN

The syndrome of hyperinsulinism was first described in 1924 by Harris (26). According to him, it may be caused by organic or functional ailments in the islands of Langerhans. The severity of these organic abnormalities may range from adenoma to carcinoma. But surprising enough, the diseased cells continue to secrete insulin and do so without the usual bodily regulation. Hence, we have hypoglycemia. In 50% of such instances, resection of parts of the pathological pancreas has relieved the condition.

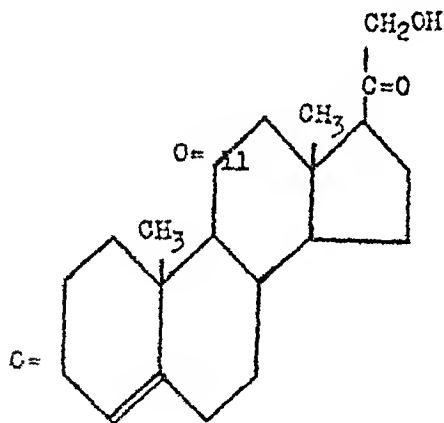
Functional hyperinsulinism is an overactivity of the normal island cells. The Finneys (27) report a patient who had recurrent hypoglycemic attacks of increasing severity. No organic cause for her malady was found. Physical examination did not reveal endocrinopathy and a laparotomy disclosed a normal pancreas. Nevertheless resection of a portion of that organ resulted in an improvement of the patient's condition.

DEFECT IN THE NEUROENDOCRINE DEFENSE

Because of the reduplication of function resulting from the activity of the several endocrine glands involved in preventing hypoglycemia, it cannot be expected that the failure of one of these glands should precipitate a fatal attack. The sympathetic-adrenal system, the emergency defense against low blood sugar is rarely rendered completely inactive by disease. In the laboratory, however, it is easy to demonstrate fatal hypoglycemia when insulin is injected into animals with one adrenal gland extirpated and the other denervated by cutting its splanchnic nerve (28).

The same principle of this reduplication of defense is effective in preventing grave hypoglycemia in hypoadrenalism. In patients with hypothyroidism postabsorptive blood sugars tend to be low but the degree of hypoglycemia is mild and of little clinical importance (29). By the same token, lesions destructive of the posterior pituitary would probably not lead to a significant decline of blood sugar. When the cortex of both adrenal glands is completely destroyed, as occurs sometimes in Addison's disease, the hypoglycemia is more severe. In this disease, not only is the diabetogenic hormone lost, but also the hormone which accelerates the formation of new carbohydrate from protein*. Welty and Robertson (30), among many others, cite two proved cases of Addison's disease which showed evidence of marked hypoglycemia with coma relieved by dextrose administration.

Another exception to this rule that the multiplicity of defense prevents a grave hypoglycemia, may be found when the anterior pituitary gland is destroyed, as seen in Simmonds' disease (31). Here hypoglycemia is likely to be profound because more than one endocrine element in the prevention of hypoglycemia is impaired. As we know, the anterior pituitary occupies a central position of influence over the other glands of the body. It follows, therefore, that any destruction to this gland would naturally concern the welfare of other parts of the body, such as the thyroid and the adrenal cortex which will suffer a secondary degeneration. When the



anterior pituitary gland no longer sends forth the thyrotropic and the corticotropic hormones to the thyroid and adrenal cortex respectively, these glands undergo regressive changes, and in general the degree of hypoglycemia depends upon the extent of their regression. The basis upon which the entire endocrine defense rests is the anterior pituitary, therefore any injury to this all-important gland would effect a more serious hypoglycemic condition than would result from partial injury of any other one gland.

*Hormones of the adrenal cortex have been isolated from the gland and also synthesized in the laboratory. In general the structure is like that of dehydrocorticosterone. It is necessary to have an oxygen atom on the 11th carbon atom in order to obtain the carbohydrate effects of the hormone.

THE SYMPTOMATOLOGY AND TREATMENT OF HYPOGLYCEMIA

Whatever the cause of hypoglycemia may be—whether it be by failure of the liver, disturbance of the endocrine defense against hypoglycemia, or too much insulin either of endogenous origin or injected—the symptomatology is always the same. Most prominent among the symptoms are those involving the central nervous system (31). These appear earliest, coming throughout the ever-moving picture of hypoglycemia and are the most dangerous. Organ systems other than the nervous system also undergo changes but when these are analyzed, they are found to be frequently secondary to those of the central nervous system. As an illustration, some of the electrocardiographic changes (32) during hypoglycemia—i.e., reduction or inversion of the T wave—may be due to a direct effect on the heart, but they also show an initial transitory excitation, a sympathetic influence followed by bradycardia due to parasympathetic predominance. These autonomic effects emanate from centers, hypothalamic and midbrain, situated within the central nervous system.

The reason for the peculiar sensitivity of the brain to hypoglycemia lies in the fact that the brain, even in diabetes, is the only organ which obtains its energy from the combustion of carbohydrate alone (33). It is well known that most of the organs in the body support their metabolism by the oxidation of both carbohydrate and fat. When, for any reason, the carbohydrate supply in the blood is decreased or interfered with, the various non-nervous tissues of the body continue to maintain their activities at the expense of energy obtained from the oxidation of fat. The brain, however, when deprived of carbohydrate can resort to no alternate foodstuff. Its metabolism must necessarily slow down and cerebral function will suffer. Studies of cerebral metabolism made before, during and after insulin hypoglycemia reveal that profound hypoglycemia

TABLE I
Effect of Insulin Hypoglycemia on Brain Metabolism

1	2	3	4	5
Patient and Date	Blood Flow Ratio	Arterio-Venous Difference Volume Per Cent Observed	Oxygen Per Cent Corrected	Brain Metabolism
Br 6/21/40	1.00	6.14	6.14	100
	0.60	4.67	3.66	59
	0.70	2.16	1.51	25
	0.90	2.34	2.09	34
	1.00	1.74	1.44	22
Br 7/15/40	1.00	6.57	6.57	100
	0.70	2.45	1.72	26
	1.00	6.62	6.62	101

Legend: Column 2 represents the ratio of blood flow before insulin to that after insulin, with 1.00 as a basic comparison value. Column 3 represents the oxygen removed by the brain from each 100 cc. of blood passing through it. When the values in column 3 are multiplied by 10 to be equal to the values in column 2, the corrected values for arterio-venous oxygen difference after correction for decrease in blood flow, and these are equal to the values in column 4. Column 5, which is a percentage, indicates the relative importance of each value of the arterio-venous oxygen difference in terms of the value obtained when the corrected values are equal to 1.00.

*Corrected after an important work of dehydrocorticosterone.

may depress the brain metabolism to one-quarter (34) of its normal rate, and that following the administration of glucose it returns to a normal value.

The work of Frostig (35) reveals that the symptoms of hypoglycemia are divisible into 5 different constellations. The first of these appear when blood sugar first falls away from normal levels, and this phase continues until the blood sugar level has reached its nadir. The remaining four phases follow successively as long as this low level persists. The five groups of symptoms are unvaried in their order. Even a large dose of insulin does not alter the sequence of symptoms though it hastens their rate of succession.

This definite order of symptoms may be explained on the basis of the metabolic rate of each region in the brain (36). The newest portions of the brain, the cerebral hemispheres and parts of the cerebellum, metabolize at the highest rate, and therefore are the first to suffer from decrease of blood sugar. Then, in turn, each succeeding lower portion of the brain becomes involved. The medulla oblongata, the oldest part of the brain, exhibits the lowest metabolic rate and continues to function long after the other higher regions are no longer able to do so.

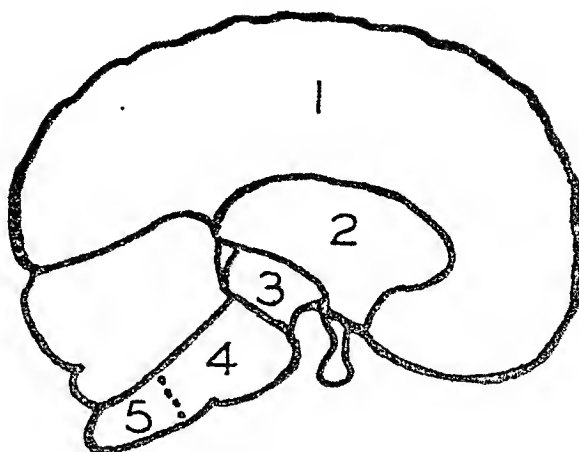
Neuropathological analysis reveals that these five groups of symptoms may be allocated to five "layers" in the brain. The first group of symptoms is referable to depression of the cerebral hemispheres and parts of the cerebellum, the highest "layer" of cerebral tissue. The second group is associated with the release of activities in the subcortico-diencephalic "layer" of the brain which is made up of three kinds of centers: subcortical motor nuclei, sensory thalamic nuclei and autonomic or visceral nuclei. The third constellation of symptoms represents the liberation of the midbrain, and the fourth phase frees the functions regulated by the upper part of the medulla oblongata. The fifth group is due to the release of the lower portion of the medulla oblongata and its vital centers, respiratory and cardio-vascular. The fifth stage constitutes a sign of danger to the patient, a contingency which will be detailed below.

It is difficult to study the symptoms of hypoglycemia when a diabetic patient is precipitated into such a condition. A doctor is not in a position to make studies at this crucial time; his one desire being to free the patient from his danger. On the other hand, in the insulin hypoglycemic treatment of schizophrenia when this condition is regularly produced as a therapeutic measure, an excellent opportunity is afforded to study the clinical picture. We have therefore detailed the series of events observed in a patient with schizophrenia who has received a dose of insulin adequate to throw him into deepest coma. As these symptoms are described, we notice a striking similarity to those which would arise if a series of successive sections were made through the various phyletic layers of the brain.

1. The Cortical Phase.

Within $\frac{1}{2}$ hour after the injection of insulin, the first group of symptoms becomes evident, and as we have said, may be allocated to a depression of cortical and cerebellar functions: sweating and salivation, mus-

FIGURE 3



LOCALIZATION OF FIVE PHASES OF HYPOGLYCEMIC SYMPTOMS:

1. Cortical
2. Subcortico-diencephalic
3. Mesencephalic
4. Premyencephalic
5. Myelencephalic

cular relaxation and tremors, are all accompanied by gradual clouding of consciousness. The latter is progressive starting with somnolence and mental retardation going on to failure in orientation and finally to complete loss of contact. Sometimes a state of wild excitement marks the end of the first stage

2. The Subcortico-Diencephalic Phase.

Loss of contact may be regarded as the onset of coma and of the beginning of the second group of symptoms, which may be allocated to the subcortico-diencephalic portion of the brain. When the subcortical motor nuclei are freed from cortical regulation, stereotyped movements become apparent. These are primitive movements such as involuntary sucking and grasping, both of which are elicited by placing an object either in the hand or between the lips of the patient. Other primitive movements which may appear at this time are kissing, snarling, and grimacing. During this time the patient exhibits ceaseless, aimless motions known as "motor restlessness." Fine myoclonic twitches of the muscles are observed, and if they become generalized and more vigorous they are transferred into clonic spasms and may be the precursors of a fit. Rarely are these convulsions seen in hypoglycemia, but if they do appear, it is almost always in the second phase.

The response to stimulation of any part of the body through this period is like that to a painful protopathic stimulus. The release of a special region in the brain, the sensory thalamus, from cortical control, is responsible for this hypersensitivity. For example, in attempting to elicit the sign of Babinski from the patient, the whole leg is withdrawn. The liberation of the hypothalamus, another subcortical region, brings about signs of preponderance in the sympathetic nervous system expressed periodically in waves of activity as the heart rate accelerates, the pupils dilate and exophthalmus is observed. The face is flushed and the body is drenched in viscid perspiration. The pupils still react to light. When these motor, sensory and autonomic symptoms begin to disappear, it is a fairly accurate sign that the patient is entering the third phase of his episode.

3. Mesencephalic Phase.

After the activities of the second "layer" have been completely suppressed, the third layer, or midbrain, is left in uninhibited control over the remaining active portions of the central nervous system. The primitive movements distinctive of the second phase cease, the patient is less responsive to external stimuli, and signs of sympathetic overactivity disappear as the balance is regained between the two branches of the autonomic nervous system. Pathognomonic of the mesencephalic phase are the tonic spasms, where the agonistic and antagonistic muscles contract simultaneously, but the increased tonus displays a postural distribution: in the upper extremities the flexors are predominant, and in the trunk and lower extremities, the extensors are prepotent. Another motor symptom is the torsion spasm, in which the body twists around its own long axis. In the midbrain are situated the nuclei of the extraocular nerves, and as a result of the loss of the regulating effect of the two higher layers, the two eyes no longer act in an associate manner but reveal movements independent of each other. An important sign of the inhibition which is lost with the depression of upper portions of the brain is the Babinski, easily elicited in the mesencephalic phase.

4. The Premyeloencephalic Phase.

We are aware that the premyeloencephalic phase is approaching when the tonic spasms of the third phase give way to extensor spasms. In this type of spasm, the back and lower extremities are arched as in the tonic spasm, but the difference is in the position of the arms. Instead of being flexed as they are in the mesencephalic period, they gradually work themselves upward and backward until all four extremities are extended in full length. These spasms are recurrent and each one lasts but a short interval. During the change in postural tone from tonic spasms to extensor spasms, the reflexes of Magnus and McKleyn may be elicited. Rotation of the head, whether spontaneous or passive, is accompanied by extensor spasms of the extremities on the side towards which the chin points and flexor spasms of both extremities on the side towards which the occiput turns. In many ways this phase resembles the picture of the decerebrate cat or dog of Sherrington with brain sectioned through the mesencephalon. The symptoms may therefore be allocated to the rostral portion of the medulla oblongata, hence, the term premyeloencephalic. This stage while not dangerous in itself gives warning of the succeeding and perilous myeloencephalic constellation of symptoms.

5. Myeloencephalic Phase.

The fifth stage, or myeloencephalic, is risky and constitutes the most dangerous point in the coma. It should not be allowed to continue more than 15 minutes or so, for at the instant it is recognized, glucose should be administered. This is the deepest phase of the coma and is recognized by the predominance of parasympathetic signs. The patient's respiration is rather the least rate is slow, his skin pale and moist, and the pupils are pin-point, no longer reacting to light. The perception is taken on a water consistency

and the body temperature which has been falling continuously, now reaches its lowest point. The patient's muscles are relaxed, tendon jerks are now depressed, and the corneal reflex is lost entirely. One gets the impression that all the life processes are slowed down to a minimum, but in truth it is actually the brain which is suffering most. Indeed any further cerebral depression would not be compatible with a complete recovery.

Recovery.

If glucose is administered at any time up to and including the first 15 minutes or so of the fifth phase the symptoms are recapitulated in a few minutes and in the reverse order of their original development (35). Once glucose is again available to support metabolism, the various phyletic layers are brought back into function, this time in a rostral direction. The *vago-tonic* symptoms of the fifth phase immediately disappear. The extensor spasms of the fourth phase may last for a brief moment before the tonic spasms of the third phase are substituted in their place. The "motor restlessness" of the second stage follows directly and the clouded consciousness of the patient gradually clears as he regains contact with his environment.

With the aid of this pattern of symptomatology, it is not difficult for the physician to appreciate the early symptoms of hypoglycemia, to recognize and fear the later ones and to evaluate properly the prognosis. If the late symptoms are misheeded and the depression is allowed to endure too long in the fifth phase, recovery is delayed and perhaps may be incomplete, or even entirely impossible—depending upon the duration of this dangerous period. The delayed administration of carbohydrate may result in a recovery, which instead of taking place in a few minutes, may require hours or even days. Sometimes neurological symptoms take hold, such as a facial palsy, and may persist over a number of days. If the destruction of the brain is widespread, death will ensue despite any treatment. In these cases pathological studies reveal disintegration and disappearance of brain cells. Both gray and white matter reveal devastation (37).

We have seen one such fatality in a patient (38) who developed insulin resistance because of an infection of his left great toe. His dose of protamine zinc insulin was accordingly increased. When his diabetic condition was under better control as a result of this large dosage, his gas pocket was cleared out, but unfortunately his dosage was not reduced and therefore the amount of insulin, which before the relief of the abscess, was just adequate, now became highly excessive. The patient after his return from the operating table fell into profound hypoglycemic coma. He was not recognized as such until many hours later, at which time he was immediately given glucose. But the treatment was too late and the patient never recovered. In the fourth phase, probably because of depressing effect of destruction. The patient exhibited tonic extensor spasms coming on periodically and he died in a few hours. Two observations of the organs involved in the brain made from blood samples collected in these spasms showed the extreme difference in the cerebral

should be reduced to about 2.5 of the normal value, in spite of the fact that his blood sugar had been raised far above normal, to 250 mgm. per cent. Had the physician recognized the early symptoms of hypoglycemia, the entire episode would have been prevented. And carbohydrate administered before the fifth phase was well underway would have insured recovery.

In cases of this type it is wise to administer a depressant drug. Sodium amytal, 17% pt. injected intravenously would have ameliorated the severity of the extensor spasm, and perhaps permitted the patient to pass successfully through the shadow of the fourth stage. Barbiturates diminish all motor activity during insulin hypoglycemia, and when given prophylactically prevent convulsions.

When we see the severity of the hypoglycemic symptoms in an adult, and the ever-present possibility of a fatal outcome, we are struck with the relative mildness which hypoglycemia evokes in the infant. Rarely are these diastolic symptoms observed in the newborn and if they are, the prognosis is generally good. It is well known that all newborn infants suffer from hypoglycemia at birth, but do so with impunity. Prosser White (38) reports a large number of subnormal blood sugars in 19 babies, yet the first only one instance of a hypoglycemic reaction. How is it possible to explain the relatively benign effects of hypoglycemia in newborn human babies? Recent investigations have disclosed that the metabolic rate of the newborn infant is much lower than that of the adult. This has been proved on lower mammals (36) and has been indicated for the human (39). A low metabolic rate has a far better chance than a high one of sustaining itself in the event of a declining blood sugar level. The brain, as we have stressed above, is like any other organ in that it functions only when it is supported by the expenditure of energy. The cerebral cortex of a newborn infant, therefore, cannot be functioning to the same extent as an adult's because the newborn expends much less energy. This being the

case, the infant should be relatively free of these symptoms which apply to the adult, and still less likely would be any cerebral damage.

Summary.

We have seen that it is important to maintain the level of blood sugar in our bodies because if it is reduced beyond the lower normal limits, the brain is deprived of its foodstuff, glucose. The relative danger of hypoglycemia may be measured by the methods which have been provided for their prevention. Only one mechanism—the parasympathetic-insulin apparatus—acts to limit a rise in blood sugar, while the symptoms working against a fall in blood sugar are many and intricate: the sympathetic-adrenalin apparatus, the thyroid and posterior pituitary, as well as the anterior pituitary and adrenal cortex. Hypoglycemia may arise from 3 general causes: (1) failure of the liver, (2) excessive insulin, and (3) a disturbance in the neuro-endocrine defense.

It has been shown that when hypoglycemia does arise, the symptoms are the same irrespective of the cause, and fall into a definite sequence of five stages. This sequence is ascribed to different metabolic rates in the various regions of the brain, the highest being found in the newest portions, and each succeeding part possessing a lower rate. Since the areas with the most intense metabolic rate will be the first to suffer upon withdrawal of energy, the earlier symptoms of hypoglycemia are allocated to the new phylogenetic layers, and each succeeding phase is localized according to the decreasing metabolic activity in the subcortical layers.

Using these 5 stages as a guide, it is possible to prevent dangerous hypoglycemia by proper treatment upon recognition of the initial symptoms. An examination of the patient will reveal his stages of hypoglycemia, and carbohydrate administered at any time before the symptoms of the 5th phase last too long will insure immediate recovery. But any delay after that time will render the prognosis more and more precarious.

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Salmonellosis Caused By The Ingestion of Ducks' Eggs

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ACUTE outbreaks of paratyphoid fever C and allied types of salmonellosis often occur in Western Europe. These outbreaks not infrequently are attributable to the consumption of foods, and especially puddings and sauces, in the preparation of which the eggs of ducks have been used. Between 1932 and 1935, for instance, 86 such outbreaks, involving 520 patients and 15 deaths, were reported from Germany alone. In the Netherlands one outbreak or more has occurred almost every year. (1) In England the disease is not uncommon. (2)

SALMONELLOSIS IN THE FOWL

Ducks, like several other birds, often are attacked by infection with some species of *Salmonella*. The acute stage of the disease occurs almost exclusively among the young birds. Many of the birds die, but those which survive spread the infectious organisms in their stools, even though residual diarrhea may not be present. The clinical signs of infection usually do not de-

velop among older ducks, once infection has occurred but such ducks nevertheless easily may become carriers of the disease. Species of *Salmonella* can be cultivated not only from the intestinal contents of the ducks, but also from the contents or secretions of other internal organs, and especially from the genital organs. Occasionally, however, the only organs from which the bacteria can be recovered are the oviducts and the ovaries or testicles. Salpingitis and oophoritis are common complications, and infection of the ovarian follicles themselves often occurs.

Clinically normal ducks can be disclosed as carriers of species of *Salmonella* by culture of the stools and also by the securing of positive results of agglutination tests of blood serum. In 1937 the latter method demonstrated that about a third of 20,000 ducks taken from one area in the Netherlands were infected. (3) In another region the rate of infection was as high as 38 per cent. About 3 per cent of all ducks' eggs on the market were found to have infected yolks. (4) However,

even when results of culture of the stools and of agglutination tests are negative, the ducks in question may lay eggs which contain species of *Salmonella*.

It has been found that pigeons also may be attacked by salmonellosis. At least one outbreak of salmonellosis of human beings in which the causative organism was *S. typhimurium* could be attributed to the consumption of pudding prepared with the eggs of infected pigeons. (5)

MODE OF TRANSMISSION TO HUMAN BEINGS

In a previous paragraph it was pointed out that infection of the ovarian follicles of ducks is not uncommon. This fact, then, explains why the yolks of eggs of infected ducks often contain species of *Salmonella*, and why such eggs, when ingested, can cause salmonellosis of human beings. To this should be added the fact that in the process of laying, the eggs of ducks pass through the cloaca, so that they are nearly always heavily soiled with stool. Hence, even when the contents of the eggs of an infected duck are free from pathogenic bacteria, contamination with *Salmonella* organisms may occur when the eggshell is broken by the cook. Clatenburg found *Salmonella*'s in 1.6 per cent of the eggs of ducks whose blood serum did not, and 6 per cent of the eggs of ducks whose blood serum did, agglutinate *Salmonella* organisms. (1) The percentage of eggs with contaminated shells must be much higher than the foregoing two figures.

Infected ducks and geese also may indirectly cause salmonellosis of human beings. The stools of infected fowls contaminate the drinking water of cattle; the organisms thus gain entry to the intestinal tract of the animal, and the meat derived from such an animal may become infected.

It should be said that the consumption of fresh eggs, even if they are laid by infected ducks, is hardly ever dangerous, because the number of organisms in one egg is small. If, however, raw or insufficiently cooked eggs of ducks are used in the preparation of ice cream, sauces, puddings, pies or mincemeat—all of which are dishes that may be put away for hours before they are consumed—*Salmonella* organisms may multiply rapidly and infection of human beings may result if the dishes are eaten. The cook who has prepared the dangerous dish usually remains well, because he or she tastes the food immediately after it has been prepared, at a time when the concentration of organisms is still small.

TYPES OF SALMONELLA RECOVERED

In Western Europe the two species of *Salmonella* especially likely to be found in ducks' eggs are *S. enteritidis* (variety from Es-en, with delayed fermentation of dulcitol) and *S. typhimurium* (with delayed fermentation of rhamnose). *S. anatis* never has been isolated in European cases of salmonellosis transmitted by ducks. In the United States *S. typhimurium* (*aertrycke*) was found in 176 of 223 cultures derived from 100 outbreaks of avian salmonellosis. (6) Twenty-two of these cultures were obtained in five outbreaks of salmonellosis of ducks, three of which outbreaks were caused by *S. typhimurium*, one by *S. anatis* and one by

Salmonella sp. (Nervington type). Subsequent to the aforementioned investigation, *S. enteritidis* has also been recovered from the stools of ducks in the United States. (7)

RANGE OF INFECTIONS AMONG HUMAN BEINGS

NETHERLANDS. In the Netherlands the danger of salmonellosis of human beings arising from infected eggs of ducks led in 1938 to the introduction of a law by which the use of such eggs in the preparation of foods or drinks is forbidden. Furthermore, ducks' eggs may not even be kept on premises where food is prepared. Finally, all ducks' eggs which are available for consumers are stamped: *Ducks' eggs—boil for 10 minutes*.

GERMANY. The occurrence of outbreaks of paratyphoid fever C and other forms of salmonellosis in Germany has been mentioned in the first paragraph of this paper. These outbreaks led to the passage and enforcement of a law in Germany similar to that passed in the Netherlands.

UNITED STATES. In contrast to the foregoing experiences in Western Europe, salmonellosis caused by the ingestion of infected ducks' eggs has been described only rarely in the United States. In this country ducks are raised almost exclusively for the production of meat, not for egg production. Brown, Combs and Wright have reported a food-borne outbreak of infection with *S. typhimurium* (*aertrycke*) in an orphanage in Kansas. (7) This particular outbreak was caused by the ingestion of a pudding prepared with the eggs of infected ducks.

ORIENT. Until recently not much attention had been given to a possible relationship between the frequent occurrence of salmonellosis in the Orient and infected ducks' eggs. But as early as 1908 Van Loghem, working in Deli on the northeastern coast of Sumatra in the Netherlands East Indies, isolated from febrile patients an organism which caused a paratyphoid-like fever, but which was different from *Salmonella paratyphi* and *S. schottmulleri*, the causative organisms of, respectively, paratyphoid fever A and paratyphoid fever B. Van Loghem designated his organism *Bacillus suispestifer Deli*. It now seems apparent that what he had discovered was the causative organism of paratyphoid fever C, or *Salmonella hirschfeldii*, which was not described until 1917 by Weil and 1918 by Newkirk. Epidemics caused by this and allied species of *Salmonella* have been reported regularly from this part of the Netherlands East Indies, (8, 9) and in later years also from Java. (10) Careful investigations in recent years have demonstrated that a remarkable number of species of *Salmonella* occur in Java. Of the different types distinguished in the Kauffmann-White scheme, 25 have been isolated in the Netherlands East Indies, and in addition to these 25, three new types have been found. (11)

Ducks' eggs are a favorite food of the Indonesian peoples of the Netherlands East Indies. Chickens of this part of the Orient lay eggs poorly, and the eggs are small. Solution to this difficulty by the importa-

economic conditions, or the stress and strain of his daily work. Individuals who have suffered long and severely become neurotic and their statements are unreliable. They need mental and psychic guidance as well as physical rest. Patients with idiopathic ulcerative colitis should be hospitalized and denied, or at least limited, as to visitors. Psychotherapy directed toward the alleviation of emotional or social problems is essential toward assuring these patients of our own confidence in the plan of treatment we are about to inaugurate.

Sedatives and antispasmodics have a definite though limited use. The literature is replete with drugs, natural and synergistic, which are said to depress the overactivity of the parasympathetic system and to thus allay nervous excitement, anxiety and apprehension. My experience with their local effects has not been satisfactory. They are tolerated by the digestive tract for only a brief period and their psychic deteriorating effect is sometimes distressing. Phenobarital, $\frac{1}{2}$ grain (0.03 gm) three times daily, promotes longer hours of restful sleep. Tincture of belladonna in doses of 30 to 45 minims (2 to 3 cc.) daily may be helpful. Camphorated tincture of opium may be indicated at the beginning of the management of the severe acute fulminating cases.

Diet during the diarrheal stage: A soft diet, high in calories and vitamins and low in residue, is prescribed. This includes bananas, cooked vegetables, bread, butter, eggs, meat and fish and a glass of milk or buttermilk (8 ounces) at each meal. It excludes raw fruits and vegetables, as well as beans, cabbage, and other notoriously "gassy" foods, candy, honey, syrup, bran, nuts, carbonated beverages, beer and spiced or highly seasoned foods. Smoking and chewing gum may also produce flatulence and should be avoided. This menu should be supplemented with liver ($\frac{1}{2}$ pound twice a week), and glandular meats for parathyroid action ($\frac{1}{2}$ pound once a week).

Diet during the convalescent stage: The health of normal people is determined considerably by the type of food they eat, and this is of specific importance in chronic digestive disturbances. Many of our chronic ulcerative colitis patients show objective evidences of nutritional deficiencies and it should be routine to look into the patient's dietary history during both the diarrheal and constipated stages, evaluating the absorption of his diet and estimating his dietary requirements. Acute deficiency states are more easily recognized than are the chronic borderline ones, and the possibility that borderline deficiency, over a long period of time, can cause ulcerative changes in the bowel, should be kept in mind. Granting that the diarrheal attack may be an infection, a food deficiency may be a secondary factor. However, at the present time, there is no proof that a lack of any specific food is a causative factor in chronic nonspecific colitis. During the convalescent stage many of these patients have a red, smooth tongue and skin changes of vitamin B complex deficiency. After the diarrhea has subsided and the bowel is functioning normally, the patient should be placed on a well-rounded and adequate diet. A detailed statement of the food taken at each meal in the day, together

with a statement of the number of times per day, week or month that the articles mentioned are eaten, and approximately what amounts, is a time-consuming but necessary feature of the diet history.

Supportive therapy: Dehydration, exhaustion and anemia are alarming complications in any type of ulcerative colitis and may occur suddenly in all cases. They are combated with:

A. Intravenous administration of 10 per cent glucose in normal saline in amounts of 2,000 to 3,000 cc. daily until the nausea and vomiting cease, the tongue becomes moist, the intense thirst is relieved and the patient expresses a desire for food. In some cases, one or more blood transfusions up to 500 cc. each may be necessary.

B. When retained fluids are given by mouth, at first guardedly, and later urged so that the patient received 3,000 cc daily. This includes water (not iced), fruit juices, coffee or tea, and soup. Milk and chocolate are withheld until later.

C. Deep gluteal injections of 1 cc. liver extract be given twice weekly.

Toxemia: As a result of the diarrhea, vomiting and ex-anguination accompanying the dysentery toxemia becomes a serious factor. Calcium has been used in tuberculous ulceration of the bowel to replenish these excessive losses which are made worse by the poor absorption through the inflamed bowel. Calcium is said to lessen the permeability of the tissue fluids from the ulcerated colon. Relief of the mucosal congestion and inflammation lessens the intestinal spasm and colic as well as the spreading of the infection, besides contributing to reparative processes by fibrosis and calcification. Mackie (1) says calcium lessens the protein hypersensitiveness or allergy of the cellular tissue. Minot (2) considers hypergnanidinemia one of the factors of dysenteric intoxication which may be relieved by calcium therapy. Calcium seems to have multiple and diverse actions on the inflamed intestine and its combined powers seem to stimulate immunizing and reparative processes. Our patients were given immunizing and reparative processes. Our patients were given calcium orally in the form of milk and of calcium gluconate, and intravenously as 10 cc. of calcium gluconate 10 per cent each day. Calcium is said to be enhanced by the associated administration of parathyroid hormone or vitamin D. Bismuth subcarbonate and kaolin, either of which is used in one teaspoonful doses after each bowel movement, has been recommended as an inert powder of high absorptive ability which mechanically will hold and carry out hordes of toxic bacteria. Sera and vaccines to relieve the toxemia, presumably by neutralizing circulating toxins, is of doubtful and then only temporary benefit.

Topical Bowel therapy.

Much has been written about chemotherapy in the various types of ulcerative colitis. The most satisfactory drugs, at present, are the sulfa preparations and iodoxyquinolinesulfonate. In this study we use Anayodin*. This preparation has been recommended be-

*The Anayodin used in this work was furnished by a grant from the Ernst Bischoff Company, Inc., Ivoryton, Conn.

cause of its definite bacteriostatic action with poor absorbability from the bowel. Carefully administered doses saturate the intestinal contents without producing a dangerous level of the drug in the patient's blood. However, active ulceration in the intestinal tract may modify the absorption of any of these drugs. Anayodin (sodium iodoxyquinolinesulfonate) with an iodine content of 28 per cent has an action on the thyroid and this should be watched. In this group no untoward effects were noticed. It should be remembered, however, it is an amebicide and bactericide. It combats the infective agent but is not able to repair the destruction to the intestinal mucosa or other organic deformity complicating the disease. Also its bactericidal action does not extend to producing an immunity to the dysenteric organism and a reinfection of the patient may occur. The intestinal flora per se is but part of our patient's discomfort. Destruction of the mucous membrane by the inflammatory process, the stenosing effect of these changes, the lack of efficient bowel drainage, the systemic effect of absorbed intestinal toxins and alterations of the normal bowel function will still remain as evidences of colitis. These several factors can be evaluated only by repeated careful laboratory studies.

Treatment with Anayodin was begun with 1 pill (four grains) every six hours the first day, 2 pills per dose the second day and 3 pills per dose for the next seven days. This was followed by a rest period for one week. Anayodin, in powder form, is a light yellow crystalline and feebly soluble in warm water. A 2 per cent solution was used as a colonic irrigation in some cases. A small amount, about 6 ounces, was run into the bowel, retained 3 to 5 minutes, and allowed to run out. This procedure was repeated until one quart of the solution had been used.

At the end of the course the diarrhea had usually ceased and the blood and mucus disappeared from the stool, and there seemed sufficient concentration of the drug in the intestinal tract to maintain definite bacteriostatic action. A rest period of one week was then allowed to guard against hemolytic anemia or other toxic reactions, and the course of treatments were then repeated a second, third and fourth time. The colonic irrigations were troublesome and were continued with but 10 patients. However, those patients in whom the colonic irrigations were given twice daily became apyrexial within 3 days.

CASE REPORTS

Space does not permit detail of all of these patients, but we shall detail:

1. An acute fulminating dysentery.

Mr. S. R., traveling man, age 56, just returned from a three weeks' trip into the flooded area of central Illinois: complained of nausea, anorexia, severe griping pains in the abdomen, and frequent bloody mucus stools in the past week. He lost 10 pounds in weight.

Examination: He acts fatigued and is dehydrated. Palpation of the abdomen elicited tenderness along the colon, more severe about the sigmoid. Proctoscopic examination demonstrated much free bleeding, mucus

and light yellow liquid stools. The bowel wall was edematous and bleeding from numerous superficial ulcerations. The proctoscope could be introduced only 20 cm. Cultures of the rectal swabbings showed *B. Coli*, and *Proteus valerci*. Indirect blood agar culture showed a streptococcus of the beta or hemolytic group.

Treatment:

1. Nothing by mouth for 24 hours. Then liquid diet.

2. Intravenously 2,000 cc. of 10% glucose in normal saline every 12 hours for 3 doses. Liquids orally thereafter.

3. Anayodin 2% solution colonic irrigation of 1,000 cc. every 12 hours.

4. Beginning on the second day Anayodin 4 grains every 6 hours, increased to 8 grain doses on the 3rd day and 12 grain doses thereafter.

By the fourth day the diarrhea had ceased, anorexia had disappeared, water and food were accepted by mouth, and his temperature was normal. He remained in the hospital one week and when he left the abdomen was free of pain, the stools did not show blood and there was no visible rectal ulceration. After he left the hospital, the rectal irrigations were discontinued but Anayodin by mouth, one pill (4 grains) after each meal, was continued for two weeks. No recurrence of the diarrhea.

2. Active chronic dysentery.

Mr. E. B., age 45, office employee, has had diarrhea for 4 years. There has been no remission of less than 6 stools per day with colicky pain. At the time of examination he was having intense diarrhea with mucosanguineous stools. Proctoscopically the rectal mucosa was edematous and extensively ulcerated. This case looked suspiciously like an amoebic infection but no trophozoites or cysts of *Endamoeba histolytica* were ever found though repeated search was made. His appetite was good and he was not dehydrated. He was put to bed, given a soft diet high in protein, low in carbohydrate. Also given 2 colonic irrigations per day of 1 quart of 2 per cent Anayodin and by mouth, Anayodin, 8 grains after each meal. At first (for 2 days) his diarrhea was accentuated and then it promptly receded so that beginning with the fourth day he had no defecation except with the irrigation. Anayodin by mouth was continued for 4 weeks after leaving the hospital. There has been no recurrence of the diarrhea after 3 months observation.

3. Recurrent dysentery.

Mrs. L. J., age 34, para 2, housewife, has had a diarrhea for the past 8 years. The stools are liquid with solid particles, sometimes with mucus and blood. They vary in number from 2 to 8 per day. There is constant abdominal discomfort sometimes definite colic. Her anus is very sore. She has been on several dietary regimens. She has lived in Florida, Texas, Oklahoma, Colorado and Illinois. Her blood morphology was:

Hemoglobin	70 per cent
Erythrocytes	4,780,000
Leukocytes	12,750

Stool examination showed innumerable yeast cells. This patient was placed on a bed rest, soft diet. Anayodin orally and in enema as outlined above, the diarrhea ceased and her abdomen became quiet. She continued this regimen and felt quite normal. All treatment was discontinued and she tried to live a normal life. After 3 months the diarrhea returned. A second course of therapy for one month brought relief, which continued for 22 weeks and she had another relapse. After a third course of therapy, we have followed with a continuous course of supportive treatment, the special diet and Anayodin 4 grains after each meal. Now after 17 weeks she is symptom free.

SUMMARY

A treatment of Chronic Ulcerative Colitis in which diet, rest and treatment with Anayodin (iodoxyquinoline sulfonic acid) has been described. Anayodin was administered orally and by enema with good results.

Three case histories, one acute, one chronic and one recurrent have been related.

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The Influence of Diet on Sulfonamide Action *

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THE study of the effects of diet on sulfonamide action (1, 2) has been extended. The data presented in this report are based on the results found in 403 rats.

Male rats, at weaning age, were placed on the special diets to be investigated. The animals were kept on the selected experimental diet for 24 to 27 days. Body weights were recorded 3 times weekly, and only the animals that made a satisfactory gain were used. Since the animals were young, they were not fasted overnight, but had access to food until shortly before the drug was given. Some rats in each group were used as controls; these received no drug. The other rats were given one dose of sulfonamide, (1 cc of 7.5% of the sodium salt per 100 grams of rat), by intraperitoneal injection. The animal was killed, by a blow on the head, 3 hours later, at which time sufficient blood was collected for determinations of blood sugar and drug level. The liver was removed rapidly and hydrolyzed as a whole; an aliquot part was taken for the glycogen determination by a modified Pfluger method.

Purina dog chow checkers was chosen as the control diet. The experimental diets studied were high fat, high protein and high carbohydrate, in which butter and oleo, casein and sucrose, formed about 87% of the total calorie value, respectively. Adequate salt mixture and vitamin supplements were added to the experimental diets. The animals gained weight on every diet, but the amount varied, as would be ex-

pected; the results are shown in Table 1.

The sulfonamides studied include the sodium salts of sulfathiazole, sulfadiazine, sulfapyridine and sulfapyrazine.

In Table 1 are shown the number of animals, days on diet, initial weight (at time the animal was placed on the experimental diet), final weight, gain in grams, gain as per cent of initial weight and liver weight.

In Table 2 are shown the blood sugar, glycogen as % of liver weight, glycogen as mg. per 100 grams of body weight, liver as % of body weight, concentration of total drug, free drug and % of free drug.

In Table 3 are shown the increase in the blood sugar and the decrease or increase in liver glycogen (mg. per 100 grams of body weight) found on the various diets after administration of each drug; these results are expressed as % change from the value for the control rats on each diet.

SUMMARY AND CONCLUSIONS

It is evident from Table 2 that the blood sugar of the control rats is constant on every diet under the present experimental conditions.

The heaviest livers, considered as per cent of body weight, were found in the rats which had eaten a high fat diet; the lightest livers were found in the rats on the control diet. On each diet, in turn, the livers of the rats which had been given sodium sulfapyridine were lightest.

When sodium sulfathiazole was administered, only a slight increase in blood sugar was found in rats on the control diet, and a more marked increase on the high protein and high carbohydrate diets. The high fat diet seemed to increase the susceptibility to some extent. A decrease in liver glycogen occurred in every case, but was most marked on the control diet. The high carbohydrate diet seemed most favorable, so far as glycogen is concerned.

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When sodium sulfadiazine was administered, there was a very slight effect on blood sugar, regardless of the previous diet. So far as liver glycogen is concerned, the high protein diet offers the least protection against the drug action and the high carbohydrate offers the

with those reported earlier (3, 4). The drug concentrations were maintained at approximately the same levels on every diet, and the greatest conjugation occurred on the high protein diet.

Sodium sulfapyridine led to an increase in blood

TABLE 1

Diet	Medication	1	2	3	4	5	6	7
Purina Dog Chow Checkers	Controls	20	26	48	124	76	158	5.91
	Sodium Sulfathiazole	20	27	45	116	71	158	5.41
		20	25	45	121	76	169	5.76
		20	27	48	123	75	156	5.35
		20	26	41	127	86	210	6.03
High Fat Diet	Sodium Sulfathiazole	19	26	47	93	46	98	6.23
	Sodium Sulfadiazine	20	26	43	91	46	102	6.84
	Sodium Sulfapyridine	20	26	46	99	53	115	6.85
	Sodium Sulfathiazole	23	26	51	97	46	90	6.13
	Controls	20	26	43	89	46	107	5.86
High Protein Diet	Sodium Sulfathiazole	20	26	51	90	39	76	4.93
	Sodium Sulfadiazine	20	26	46	85	39	85	4.76
	Sodium Sulfapyridine	20	24	47	89	42	90	4.51
	Sodium Sulfathiazole	20	26	47	91	44	94	4.59
	Controls	20	27	47	102	55	117	5.29
High Carbo- Hydrate Diet	Controls	20	26	51	103	52	102	5.13
	Sodium Sulfathiazole	20	26	49	92	43	88	4.66
	Sodium Sulfadiazine	21	27	49	90	41	84	4.62
	Sodium Sulfapyridine	20	27	49	91	42	86	4.52
	Controls	20	27	51	109	58	114	5.55

1. Number of rats
2. Days on diet

3. Initial weight
4. Final weight
5. Gain in grams

6. Per cent gain
7. Liver weight in grams

TABLE 2

Diet	Medication	1	2	3	4	5		
High Fat Diet	Controls	107	3.81	183.2	4.72	a	b	c
		109	2.16	101.7	4.68	1.2	1.2	100.0
		106	2.89	138.7	4.75	25.5	28.4	89.9
		158	1.36	59.4	4.32	95.7	100.7	95.0
		117	2.68	128.0	4.75	49.4	54.1	91.2
		104	1.46	94.8	6.71	86.6	91.5	94.6
		133	1.09	78.9	7.54	.8	.8	100.0
		106	1.04	69.0	6.91	29.7	33.5	68.9
		250	1.06	64.7	6.33	110.0	116.8	94.1
		117	.96	62.9	6.61	54.2	58.0	93.4
High Protein Diet	Controls	104	2.16	119.6	5.45	90.0	94.2	95.6
		124	1.59	88.2	5.59	1.1	1.1	100.0
		99	1.42	75.1	5.07	26.3	31.3	84.1
		176	1.30	66.8	5.06	92.6	96.2	96.4
		124	1.47	80.1	5.18	40.7	47.5	85.8
		105	3.94	203.9	4.98	84.8	89.0	95.2
High Carbo- Hydrate Diet	Controls	123	3.47	182.3	5.09	.9	.9	100.0
		105	4.05	208.8	5.12	22.3	24.3	91.8
		158	2.63	133.1	4.93	108.3	110.9	97.7
		130	4.44	227.2	5.11	53.4	57.2	95.4

1. Blood sugar
2. Glycogen as % liver weight
3. Glycogen as mgm./100 gms. body weight
4. Liver weight as % body weight

5. Drug level in blood
a. Free drug—mgm./100 cc.
b. Total drug—mgm./100 cc.
c. % free

most protection. The blood levels are highest after administration of this drug.

Sodium sulfapyridine had the most pronounced effect on both blood sugar and liver glycogen. The increase in blood sugar was marked on every diet. The high fat diet seemed to render the animal particularly susceptible to the action of sodium sulfapyridine on blood sugar. The decrease in liver glycogen was marked in every case, but was greatest on the control diet. The striking effects of sodium sulfapyridine are in accord

sugar in every case; this was most marked on the high carbohydrate diet and least on the control diet. The decrease in liver glycogen was quite constant on the control, high fat and high protein diets; an increase was found on the high carbohydrate diet. This drug resembles sodium sulfadiazine in that the blood level remains high and its effect on liver glycogen is similar; however, it does affect blood sugar, which is not characteristic of sodium sulfadiazine.

TABLE 3

Medication	A				B			
	1	2	3	4	1	2	3	4
Sodium Sulfathiazole	2.0	28.0	19.0	17.0	-44.4	-16.7	-26.2	-10.6
Sodium Sulfadiazine	1.0	2.0	4.0	0	-24.0	-27.0	-39.0	+2.4
Sodium Sulfapyridine	47.7	140.0	68.8	50.5	-67.0	-31.0	-44.0	-35.0
Sodium Sulfapyrazine	9.3	12.5	19.2	24.0	-30.1	-33.7	-33.9	+11.3

A. % rise in blood sugar
 1. Control diet
 2. High fat diet
 3. High protein diet
 4. High carbohydrate diet

B. % change in liver glycogen
 1. Control diet
 2. High fat diet
 3. High protein diet
 4. High carbohydrate diet

Although the sulfonamide drugs exert some effect on carbohydrate metabolism, the changes in blood sugar and liver glycogen are not parallel; two different mechanisms seem to be involved.

Sodium sulfadiazine with a high carbohydrate diet seems preferable to others, if one wishes to avoid changes in carbohydrate metabolism during the administration of sulfonamides.

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Digests

Peptic Ulcer and Dyspepsia In The Army

By

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THE incidence of dyspepsia of all types in the war of 1914-1918 was low. The prevalence of dyspepsia, organic and functional, in the Army in the present war, is not due to an increased incidence caused by the war, but is to be regarded as a reflex of its incidence in the civilian population, which has greatly increased in the past 20 years. There is no evidence of the undue development of fresh cases of peptic ulcer after entering the army. Of admissions to hospitals for peptic ulcer in 1942, the onset of the diseases occurred in civilian life in 81 per cent. Of admissions during the same year for dyspepsia not due to peptic ulcer, the onset occurred in civilian life in 75 per cent. The number admitted to hospitals for minor digestive symptoms in the Army gives an exaggerated picture of the prevalence as compared with civil life, because symptoms due to pre-existing peptic ulcer tend to recur in the Army, owing to unavoidable routine, and will recur under the best conditions of diet and cooking. Of admissions to hospitals for dyspepsia, peptic ulcer formed 58 per cent and non-ulcer dyspepsia formed 42 per cent.

Men suffering from real peptic ulcer are not suitable for life in the British Army under present conditions. Men suffering from indigestion due to other causes can in many cases make useful soldiers provided they are not detained too long in the hospital. Cure of symptoms ought not to be attempted because an excess of medical care and investigation results in exaggeration of symptoms and repeated admissions to hospital. There appears to be a rarity of complications of ulcer in the Army, as compared with hospital admissions of comparable age-groups in civilian hospitals, but this ap-

parent rarity is not real. The low mortality from hemorrhage and perforation is similar to that in civilian males under 40 years of age. The comparative incidence of indigestion between male and female personnel is similar to that among civilians.

The types of indigestion occurring in the Army may be classified as follows—(1) Peptic ulcer, (2) Gastritis and functional dyspepsia, (3) Miscellaneous group.—a small group divided among the diseases, cholecystitis, appendicitis, duodenal diverticulum, and cancer of the stomach. There is a *transient dyspepsia* affecting men soon after their admission to the Army, and usually well taken care of by the unit medical officer. These cases ought not to be hospitalized or sent to specialists because of the danger of converting them into chronic dyspeptics and useless soldiers.

"Functional dyspepsia" refers to symptoms due to physiological disorders without evidence of organic background. "Gastritis" is now used with a technical meaning by gastroscopists, and should be reserved for this. Eighty per cent of the functional cases date back to civil life with an average duration of seven years. While gastroscopy reveals a small percentage of organic gastritis, I am not persuaded that clinical syndromes can be connected with the different types of gastroscopic gastritis, in spite of statements to the contrary. The radiological diagnosis of *duodenitis* is again something that has not been satisfactorily connected with clinical facts or with pathological studies and indeed the radiologists often disagree about it. Possibly the term indicates at times uncertainty as to whether an ulcer is or is not present.

Of the functional cases, some are due to disturbance of function, some are psychoneurotics, and others become psychoneurotic. These cases are resistant to treatment, and the longer they are kept in the hospital, the sooner they are readmitted, because return to the stress of duty causes relapse. After at most 10 days' investigation, provided organic lesions have been ruled out, these functional cases ought to be returned to full duty and normal Army diet, and dealt with by the unit medical officer, who by observation can decide whether or not the man should be retained in his unit or category.

Too much expert investigation in hospital has a bad reflex effect on the functional case. Gastroscopy ought to be reserved for cases in which neoplasm is suspected, or in which one suspects an ulcer which was not radiographically revealed. In the Army it should not be used for the identification and classification of gastritis, as in civil life. If the unit medical officer will keep these men on duty, many of them become injured and are thus saved for the Service. The medical officer, through ordinary examination, may occasionally miss an ulcer, but the Army expects occasional mistakes, and, in practice, catastrophies are rare. These functional cases in civil life are those whose careers are marked by frequent absences from work. In the last war, among British troops, functional dyspepsias, like ulcer, were not prevalent.

Many functional cases are retained in the Army because the medical officer cannot recommend their discharge for non-ulcer dyspepsia, but some of them are

Army life. Were all these cases truly cases of ulcer? Or could Army cooking have something to do with it? Both these questions were settled in the negative: it was found that they were actually cases of definite ulcer, and that the majority of them dated back many years in civilian life. Naturally, of course, Army cooking did precipitate breakdowns. Even with the newer recruits coming into service, the flow of peptic ulcer cases continues. Why is it that in the last war, with as good cooking as now, the rarity of ulcer was so often remarked? Up to the end of 1915, the discharges from the Army for "inflammation and ulceration of the stomach" were 709. In the present war, up until December 1941, the number discharged for peptic ulcer was 23,574. Table 1 shows the present position of peptic ulcer, through the breakdown of 800 medical cards taken at random from the first four months of 1942:

The main supply of peptic ulcer in the Army is still the recurrence of symptoms which started in civil life and the position is similar for non-ulcer dyspepsias. The policy of the British Army is to invalid from service all men with accepted diagnoses of peptic ulcer, with exceptions in the case of key men. In the Army it is not feasible to form a special unit of service for acceptance of ulcer patients, because it entails dietary measures impossible on a scale suitable for so large a class.

The diagnosis is important because a diagnosis of peptic ulcer is permanent. The diagnosis today rests

TABLE I—Analysis of 800 Army Medical Cards of Peptic Ulcer (Random Selection from Military Hospitals in Britain; Early 1942)

Onset of Symptoms	Total				Under 40 Years				Average Age		Duration of Symptoms	
	Cases	Simple	Haemorrhage	Perforation	Cases	Simple	Haemorrhage	Perforation	Yrs.	Mths.	Yrs.	Mths.
Gastric ulcer:												
Civilian	105	98	3	4	92	85	3	4	32	7	7	4
Service	39	24	4	11	33	20	4	9	31	5	-	7
Total	144	122	7	15	125	105	7	13	32	0	5	6
Duodenal ulcer:												
Civilian	543	519	14	10	472	451	14	7	32	2	6	6
Service	113	96	5	12	100	85	5	10	30	6	1	6
Total	656	615	19	22	572	536	19	17	31	11	5	7
Total peptic ulcer:												
Civilian	648	617	17	14	564	536	17	11				
Service	152	120	9	23	133	105	9	19				
Total	800	737	26	37	697	641	26	30				

quite useless as soldiers, and many are discharged when they have been sent to a psychiatrist and diagnosed as psychoneurotic. Some, however, are unfit for Army service because of the disability caused by their dyspepsia, and should be discharged.

The medical profession was taken by surprise by the large number of admissions to hospital diagnosed as suffering from peptic ulcer as early as October 1939. The profession had failed to recognize the extent to which the various dyspepsias had increased among the civilian male population during the past 20 years, and they assumed that the influx was due to the effects of

too largely on the opinion of radiologists, not all of whom have had enough experience in gastroenterology. The doubtful radiological opinion is sometimes accepted as conclusive by a physician who is himself in doubt. I believe that at times cases which are at least doubtful both radiologically and clinically are being given the definite diagnosis of peptic ulcer. The position must not be regarded too strictly from the point of view of the gastric specialist. The essential duty of a medical board is to decide if a man will make a "useful" soldier in any category. I do not believe that the Army is losing many useful men because of gastric disabilities.

Notes on Nutrition

Nutritional problems emphasized by the war (communication from Colonel Paul E. Howe, Sanitary Corps, A.U.S.). We need to know more about how war conditions affect the nutrition of the active soldier. Are there any nutrients or combination of nutrients that will permit the soldier to overcome the effects of altitude, heat, cold, physical fatigue, recovery from infection or wounds, or the nervous exhaustion of noise or extreme excitement? The effect of heat, humidity or cold on the appetite is an important problem. The dramatic disclosures of studies on vitamins have conditioned medical men to think of vitamins as of foremost interest, but there are reasons suggesting that we re-examine our knowledge of proteins, amino acids, fats, carbohydrates, and energy requirements under conditions which eliminate the effects of insufficient quantities of other nutrients. The purification of vitamins and amino acids has opened up the field of investigation of their effect on man and on his requirements. *The saturation test* has been used in evaluating the needs of individuals and as a base line for evaluating the lower levels in body fluids. Saturation of an individual with particular nutrients indicates the maximum intake that is probably effective unless this concentration results in a modification of the effects of other vitamins or in the body processes. *Comparative nutrition* as an avenue of approach to the study of man's requirements holds out much promise. Promising investigations include the study of the relation of individual nutrients to body function, the effects of combinations of various nutrients, and the influence of nutrition, adequate and inadequate in preventing, causing or modifying fatigue, physical fitness, stamina, aging, and general health.

Loss of vitamins in sweat. Experiments show that the loss of the vitamins due to sweating is not sufficient to affect adversely an individual whose dietary intake is adequate according to accepted standards. Those vitamins which were tested were ascorbic acid, thiamin, riboflavine and pantothenic acid. Profuse sweating was induced by heat and increased humidity and exercise and samples were collected in stainless steel pans and analyzed by satisfactory methods. This information was particularly needed because of the profuse sweating of soldiers on active service in tropical regions (J. Biol. Chem. 148, 359, 1943). Other experiments (J.A.M.A. 122, 426, 1943) included niacin, with similar conclusions, but indicated that thiamin may be lost in serious amounts in sweating. At present it would appear that no very good case has been made out for serious loss of vitamins through sweat and that the extra administration of vitamins to persons constantly engaged in occupations which cause sweating is scarcely justified.

B-vitamins in sprouted cereal grains. Many reports have shown that the seeds of cereal grains, which are notably lacking in ascorbic acid, can develop significant amounts of this vitamin if they are allowed to sprout. Soybeans, most varieties of which are inedible, may

in some cases be rendered edible as human food through germination. In the sprouting of oats, wheat, barley and corn, the thiamin content changes little, but there is a marked increase in values for riboflavine and niacin. (Science, 97, 562, 1943). Increases also were noted in the values of biotin, pantothenic acid, pyridoxine, folic acid and inositol. It is evident from these results that the possibilities of making full use of our available cereals still remains to be explored.

Inanition and blood cell formation. Bone marrow can be rendered hypoplastic by starvation with a resulting hypoplastic anemia. The question as to whether this effect is due to starvation *per se* or to specific inadequacies can hardly as yet be said to be settled. Specific deficiencies in the B-vitamins are known to cause profound blood changes. Folic acid has a definite function in maintaining normal bone marrow (Science, 97, 404, 1943). Yet it has been shown that significant changes in the blood of rats can be produced by feeding nutritionally adequate diets of inadequate amounts. Inanition itself is now known to produce a leukopenia, unrelated to any deficiency in the known vitamins (J. Nutrition, 25, 511, 1943).

Nutritive value of butter fat. Is butter fat of higher nutritive value than certain vegetable oils? If so, is this because butter fat contains some saturated fatty acid or acids of high molecular weight? Could it be that such superiority, if suggested, might be due to the association of lactose with the butter fat? No difference was noted when sucrose was the sole source of carbohydrate, whether butter fat or vegetable fat was used. In feeding rats which had been deprived of mother's milk at an early age, butter fat gave much better growth rates than vegetable oils. (J. Dairy Sci., 26, 429, 1943). However, with most carbohydrates, corn oil fattened better than butter fat, but when lactose was used, butter fat was the better food. The conclusion was that butter fat must contain an unknown specific compound or compounds which, in the presence of lactose, possesses growth promoting properties. However, changes in the intestinal flora due to lactose may be of importance. The basic conclusion was that "nature has put lactose and milk fat together as an optimum combination for the young animal."

Vitamins and the growth of tumors. The whole question of the relation of vitamins to human cancer is far in the future. At present it has been found, in experiments with azo dye hepatic tumors, that the use of liver, yeast, milk and mixtures of certain grains retards the incidence of the tumors. Casein and riboflavine have the same effect. A diet low in calories also reduces tumor incidence. Recent work showed (Cancer Research, 3, 296, 1943) that large amounts of riboflavine in the diet prevented the development of the tumors; a reduction in the amount of pyridoxine fed likewise largely prevented tumor development. In sarcoma, (Am. J. Cancer, 37, 54, 1939) tumor growth

was twice as great when pyridoxine was present in the diet.

Influence of biotin upon susceptibility to malaria. The study of biotin deficient chicks and ducks after inoculation with two different plasmodia, suggested that biotin deficiency tends toward a more severe infection. The problem, even as an experimental study, is too complex to afford us definite information but the results are interesting and stimulating (J. Exp. Med. 77, 557, 1943).

Metabolic changes during shock. When shock was induced in rats by bleeding, it was found that recovery was associated with a rise in blood amino acids. The rise in blood amino acids only began to appear when the mean effective blood pressure had fallen to between 80 and 90 mm of Mercury.—and it may be assumed that the state of the liver circulation had much to do with this metabolic change. Blood sugar rises in shock only when there is a good supply of glycogen in the liver. Epinephrine plays a role in this hyperglycemia of shock, since in animals in which the suprarenal medulla had been removed there was no rise in blood sugar during shock.

Anti-gray hair factor. Few problems have occasioned such battles of opinion and contradictory reports as the problem of the influence of dietary factors on the color of the hair. A reliable and well controlled experiment (Proc. Soc. Exp. Biol. Med., 53, 47, 1943) on 19 persons with gray or white hair, showed that in only two of them did an actual change in color of the hair occur. Their hair turned dark over an 8 month period of feeding with brewer's yeast, calcium pantothenate and para-aminobenzoic acid. Any reports of results of more positive nature have always been denied by further investigations.

Experiments with radioactive sodium. The chief value of these studies thus far lies in the discovery that the antrum of the stomach absorbs a hundred times as much per unit surface as the acid secreting body of the stomach (J. Clin. Invest. 22, 103, 1943). The rapidity of the absorption of sodium was shown by the fact that appreciable amounts of radioactive sodium were found in breast milk within twenty minutes after administration (Proc. Soc. Exp. Biol. Med. 52, 223, 1943). It is also important to know that sodium is actually absorbed from the stomach itself.

Etiology of blacktongue. Experiments with canine blacktongue shows that when the disease is produced by the nonpurified Goldberger diet the animals undergo tremendous weight loss at the time of the appearance of the mouth lesions, and that many of them recover after the administration of saline, dying later without oral lesions; but when the disease is produced by a purified diet very poor in niacin, they do not experience the profound weight loss, and some of them die without ever developing blacktongue. It would appear, therefore, that blacktongue does not necessarily accompany fatal niacin deficiency in the dog, and that the manifestations of blacktongue in dogs fed a purified diet are different from those in the Goldberger type of disease. Since the Goldberger diet contains corn meal, there is the possibility of some factor in corn having

etiological importance in the disease. This is hard to atone with the fact that not all human patients with pellagra eat significant amounts of corn (Proc. Soc. Exp. Biol. Med. 52, 263, 1943).

Amino acid composition of animal protein. The importance of protein in the diet is well known, and it also has become known that of the amino acids, ten are essential and indispensable in the diet of the rat. Recent researches have indicated that all of these ten, with the exception of histidine and arginine, are also necessary in the diet of man. Recently careful analysis of the amino acids in meat proteins using the best analytical methods (J. Biol. Chem. 148, 431, 1943) shows that in the muscles of all animals and edible fowl and fish, the proportions of amino acids making up the proteins are constant, and are in the following order: for every 10 molecules of lysin, there are approximately 9 of serine, 7 each of arginine and threonine, 4 each of phenylalanine and tyrosine, 3.5 of theonine, 2.5 of histidine and about 1 each of tryptophane and cystine. Meat furnishes the nutritionally "best" source of protein because of its high biological value, and when cereal or other sources of protein are used for the bodily needs, larger amounts must be eaten to obtain the needed amount of amino acids, because it is the amino acids themselves which are basic to tissue synthesis.

Pyridoxine in dermatology. Using a method of assay for pyridoxine which has not been proved accurate, some clinical observers describe some wonderful results in the treatment of seborrheic dermatitis, atopic eczema and eczematous eruptions of unknown etiology. It is felt by the reviewer that their presentation fails to offer any convincing evidence that injections of pyridoxine exert any beneficial effects on these diseases (Arch. Dermat. Syph. 47, 651, 1943).

Further studies on the natural tocopherols. New fields of investigation with respect to glyceride, sterol and fat soluble vitamin, have been opened up by the isolation of pure alpha-beta-, and gamma-tocopherols from wheat germ oil and cotton seed oil, using techniques of molecular distillation and chromatography (J. Am. Chem. Soc. 65, 918, 1943).

Treatment of familial idiopathic with ascorbic acid. Although idiopathic and familial type is very rare, it is of interest that ascorbic acid in moderate doses apparently cures the disease, probably by combining with and oxidizing the abnormal pigment to normal hemoglobin (Brit. Med. J., I, 721, 1943).

Nutritional Principles of Mass Feeding

The problem of feeding large armies, as well as the new outlook on the feeding of populations throughout the world, has made it necessary to scrutinize not only the efficiency of production and transportation of food, but also the validity of nutritional principles, which have long been accepted. Some of the problems have been discussed recently by Captain Berryman and Colonel Howe of the Sanitary Corps (J. Am. Med. Assn. 122, 212 (1943)).

An important practical consideration is the "indispensability" of any single food item or food class. The

extent to which one food can be substituted for another should be appreciated, and from this standpoint the unique contribution of the food to the diet, or its special function therein, must be considered as well as the actual nutritive content. Obviously also, the actual amount of a given food which is likely to be consumed is as important as its quality. For example, although Irish potatoes are not nearly as good a source of vitamin C as strawberries, the former are consumed in so much larger amounts than the latter that the contribution of the potato to the diet even in regard to vitamin C is an important one.

Berryman and Howe publish a useful *Food Substitution Chart*, as well as a table indicating the nutritional contribution of various classes of foods, based on food prescribed for the United States Army (Field Ration A). From the standpoint of nutritional contribution, it is significant that meats contribute to *nine out of twelve* important nutritive components, milk products to *five*, grain products to *eight*, and potatoes to *two*. It is noteworthy that eggs, while contributing certain amounts of many nutritive components, are actually, for the soldier, a good source of riboflavin only. The maxim "eat one egg almost every day" therefore, assumes less importance since the riboflavin can be obtained by the addition to the diet of small extra quantities of liver, whole grain products, or riboflavin-enriched flour. The maximum "eat two vegetables every day, one of which is leafy green or yellow" is important particularly because of the provitamin A and ascorbic acid, as well as the iron content of such foods. If all leafy green or yellow vegetables were removed from the diet specified as Field Ration A, the planned level of vitamin A would still be much higher than that recommended by the National Research Council. Vitamin C would also remain at acceptable levels.

If we should not eat "one citrus fruit a day," the chief loss would be in vitamin C. Such a loss might be offset by the consumption of tomatoes, potatoes, and sprouting legumes or grains.

Grain products are important sources of essential nutrients and a reduction in intake would affect the caloric and thiamine levels especially. Fats, sugars, or syrups might replace the former, and thiamine could be obtained by an increased intake of meats, legumes, eggs, and certain vegetables. However, a drastic decrease in the consumption of grain products is unlikely. An imminent possibility is a reduction in the intake of meat. It has been recommended to "eat one serving of meat (or fish) every day." Should the meat content of Field Ration A be reduced from 0.85 to 0.4 pounds per man daily, the caloric intake would be reduced about 500, the protein by about 30 g., phosphorus by 300 mg., iron by 4 mg., thiamine and riboflavin by 0.4 mg. each, and nicotinic acid by about 10 mg. While this appears to be a serious loss, it is noteworthy that the decrease in protein would still leave a level of 100 g. of protein which is above the recommended daily allowance of the National Research Council. If the loss of meat can be offset by an increase of eggs and milk and of grain products and legumes, the intake of protein, as well as of certain of the B-vitamins,

would be largely made up. It is important that the public should know that the most practical way of offsetting a decrease in available meat products is by increasing the consumption of grains and potatoes.

A change from the tenet "one pint of milk a day per person" is not easy to accomplish, since milk and milk products are very important for supplying calcium and riboflavin. Nevertheless, even this maximum can be modified.

There are many difficulties which arise when food substitution is attempted, not the least of which are established food habits and palatability. It is to be noted that Berryman and Howe, like most persons experienced in the field of nutrition, do not favor the growing habit of taking vitamin pills as a means of correcting possible deficiencies in diet. Routine use of such products is rarely necessary, nor is it economical.

It is fortunate that so much thought is being given to the practical details of nutrition. Recent international conferences have made clear the ambition of the United Nations to make nutritional improvement an important goal in postwar planning. To carry out this task, a plan which gives attention to efficiency, economy, and substitution is important. Increased public interest and better distribution of essential food among the various classes of the population through limited government control, rationing, and increased purchasing power, may result in a better general state of nutrition than existed before the war. According to Youmans (*J. Am. Med. Assn.* 122, 11 (1943)), this seems to be the situation in England.

Effect of fat on calcification. It appears that fats, free of vitamin D, may exert either a beneficial or a harmful effect on calcification. It is harmful when the dietary phosphorus is low, beneficial when the dietary phosphorus is optimal. Furthermore, fat does not aid calcification when fed to animals which are receiving a high-phosphorus, low-calcium diet. Its effect is clearly different from that of vitamin D, but is not otherwise understood. (*J. Nutrition*, 25, 479, 1943).

Color blindness and vitamin A. The results of trials in which vitamin A has been given in moderate to large doses to color blind persons seem to be quite negative. No improvement could be shown to have taken place (*Science*, 95, 554, 1942) (*Science*, 97, 561, 1943).

Possible interdependence of the B-vitamins. Our knowledge of the effects of the various vitamins on each other is limited. There is reason to believe that thiamine mobilizes riboflavin in the liver and during mobilization some riboflavin is excreted by the kidneys. (*Am. J. Med. Sci.*, 205, 852, 1943). There is as yet no evidence that the use of a single vitamin ever does cause excessive loss of other vitamins, because the use of a single vitamin, in case it is lacking in the diet so stimulates appetite as to cause a salutary increased food intake.

Parenteral feeding. Although only about one-fourth to one-third of the body's daily caloric requirements can be supplied through rectal feedings, it has been shown that it is profitable at times to administer per rectum salt, water, dextrose and amino acids (*Arch.*

Dis. Childhood, 18, 22, 1943). Much progress is being made in the use of amino acids intravenously in America. (Medicine, 22, 73, 1943).

Cod liver oil and the production of vitamin E deficiency. Cod liver oil aggravates the symptoms of vitamin E deficiency in rabbits and guinea pigs, except when the cod liver oil has been hydrogenated before adminis-

tration (J. Nutrition, 15, 367, 1943). Cod liver oil or other fats, when they become rancid bring about the destruction of vitamin E by autoxidation. (J. Nutrition, 23, 625, 1943).

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Editorial

THE JOURNAL GOES TO WAR

THE Government is to be congratulated on seeing the importance of maintaining medical journals during the war period. Any pressman or linotype operator working in a printing plant which produces a scientific journal is regarded as an essential laborer, subject to the restrictions which govern his changing jobs. Enough paper is permitted the journal for all practical purposes, in amounts approximately equal to pre-war usage. The great trouble is manpower. A journal which does not possess its own printing plant may suddenly find it has to change printers, and this has occurred during the past year with this periodical. Contracts are only as good as the ability of the contractor to deliver. There is nothing he can do when most of his skilled labor volunteers or is drafted.

During the past year the costs of production have risen sharply and this fact, along with the need of reducing the manpower used in production of the journal has made it necessary to reduce the number of pages in the journal. Cuts will be, on the whole, smaller. There will be fewer sample journals to send out to those who want them. Authors may be restricted to some extent on the number of reprints which can be supplied to them. The total tonnage of paper is reduced 15 per cent, and its weight also reduced, but it is still excellent for type and cuts. In spite of all this, the subscription price will have to remain the same as now.

Nobody knows better than a medical editor the present, unprecedented difficulty in obtaining original contributions. Medical men of military age are mostly in the armed services, where their opportunity to write scientific articles is reduced practically to zero. The older men at home are engaged in strenuous teaching work or in practices swollen by the absence of their younger colleagues. Research work in the universities is reduced, except as it applies to war problems. There is not the flow of articles which usually fills the editor's basket. Actually, it is difficult to get enough original contributions to carry on. This deficiency can, with the reader's indulgence, be made good to a certain extent by reviews, abstracts and general articles, and even at times by copying of articles of unusual interest. From letters received, it appears that *all our readers thus far contacted*, prefer that the American Journal of Digestive Diseases should adopt this policy rather than suspend publication. Some of them believe that

this journal fills an important if not indispensable niche in the scheme of American medical publication, especially since it is now an independent organ without affiliation with any formal medical association.

We are going to carry on, and we hope that the reader will realize that while war has made its impression on medical periodicals, brighter days lie ahead. We need articles and reviews. If you can help, let's hear from you.

Beaumont S. Cornell.

POST IRRADIATION DAMAGE OF THE SMALL INTESTINES FOLLOWING TREATMENT OF GYNECOLOGICAL CONDITIONS

THE benefit of deep x-ray therapy or radium therapy in gynecological conditions is widely recognized. Due to the proximity of the organs, however, complications of radiation therapy cannot always be avoided. These side effects on other organs than the ones which have been originally submitted to this therapy have not been as widely discussed as it seems necessary. This is due partially to the difficulty in substantiating the findings by biopsy controls. On the other hand these lesions, artificially produced by our therapy, are not generally discussed or widely publicized. However, some authors have recently studied the effects and made known some very striking results.

The lower intestinal canal and some parts of the small intestines are in the immediate vicinity of the uterus. It is not astonishing that the aforementioned organs occasionally receive some of the radiation that was meant for the uterus. We have only limited knowledge of the amount of irradiation which the normal bowel can tolerate and we know still less as to what extent the bowel is able to recuperate from damage due to radiation therapy. We can, therefore, be only too glad that Wigby studied exhaustively these questions.

Wigby differentiates the bowel complications from a clinical point of view as follows: There are those cases in which the bowels show no reaction whatever; there are those with only diarrhea (first degree reaction); and there are those passing blood with frequent stools (second degree reaction) and those developing strictures of the gut necessitating colostomy (third degree reaction). The first degree reactions show hyperemia (often with telangiectasis) and bullous edema as seen by proctoscopy. This reaction usually begins during

the third week of roentgen treatment, although it may occur months or even years after completion of the radiation. This type of reaction generally heals without medical treatment. The second degree reactions are those in which, besides the signs of the first reactions, proctoscopy shows some ulcerations with many bleeding points. Rectal pain is fairly common. There may be typical punched-out, single round ulcers or multiple ulcers of a "beefy" red appearance and a temporary stricture may occur. The medical treatment is that of a severe proctitis. The third degree reactions are those which progress to fibrosis, affecting one or all intestinal coats. Whichever degree of fibrous stricture results, it will be permanent except for the dilatation which may be accomplished by the fecal stream. Surgery is indicated in the majority of these cases.

Extreme fibrosis of the posterior half of the pelvis is encountered frequently. Some of those who experienced reactions had received more treatment than certain of those suffering severe third degree reactions. Even by staying well within the limits of accepted dosage, reactions occur several months as well as years later without having any immediate reactions after treatment. Very often, the symptoms of this reaction may be mistaken for the hopeless recurrence of the carcinoma. Roentgenologically it is difficult to differentiate these artificially produced strictures from those due to recurrence or progression of the carcinoma. Radiation changes in the bowel, however, tend to affect a larger section of the bowel, than a recurrent neoplasm. Important also is the loss of elasticity due to wide-spread fibrosis. The clinical signs are those of chronic bowel obstruction or intractable diarrhea.

Wigby's report deals with 77 cases. Fifty-seven per cent had clinical evidence of large bowel reaction. This is a very high percentage and it is of the greatest importance to be aware of this alarming fact. Luckily only 6 cases or 8% needed a colostomy. The rectal bleeding in some cases never disappeared even after prolonged treatment. The roentgenograms, which Wigby publishes, deserve our greatest interest.

Pathologic anatomical studies of such conditions are discussed by Warren and Freedman with distinct primary and secondary criteria to support the diagnosis. The primary points to be looked for are hyalinization of the connective tissues; abnormal fibroblasts; telangiectasia and hyalin degeneration of the walls of the blood vessels. The secondary diagnostic features include the endothelial abnormalities, phlebosclerosis, the changes in the muscle fibers and the epithelial alterations. The micro-photographs which the authors publish are especially enlightening.

Hyalinization of radiation reaction may be simulated by the hyaline fibrous tissue of chronic inflammation, but with experience the peculiar swollen, glassy, fibrillar matrix of radiation reactions can be fairly well distinguished. Rapidly proliferating fibroblasts in organizing and healing processes and in active granulation tissue somewhat resemble those seen in radiation lesions. However, in radiation reactions they are less abundant, show little mitotic activity and tend to be

stellate and large rather than of the narrow spindle-shaped variety. Abnormal nuclear forms, too, are rarely seen in other than radiation reactions. Telangiectasia involving the veins and lymphatics to a marked degree is very characteristic. It may even be seen in the gross specimen or in the lesion itself prior to removal. The hyaline degeneration of vessel walls requires no further comment, although the frequent presence of ordinary arteriosclerosis in the tissues of individuals from the higher age groups may be confusing.

We want to draw the attention of the gastroenterologists to this problem, for radiation therapy has become very widely used for benign and malignant conditions. The side reactions generally reported (Wigby, Svien and Dixon, White, Jones, Cathie, and others) are those of the serious type. These observations should become much more widely known for the benefit of our patients. Besides these damages to the intestines, milder reactions occur in a very great number of patients; reactions which have not necessarily led to obstruction or perforation of the bowel but which result only in wide-spread solid adhesions. These cases show up more and more frequently in the office of the gastroenterologist. He may be astonished to find them and might have difficulty in explaining those findings in case the patient has not given a detailed history of conditions for which he has been treated by another specialist. Post-irradiation damage, thus, will gradually become an important new field in gastroenterology.

Franz J. Lust.

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IS "GASTRIC FAILURE" A USEFUL CONCEPTION?

DOES the stomach ever actually fail? If so, when and why? Naturally cancer of the stomach produces gastric failure, but this is overshadowed in importance by the fatal significance of the lesion itself. In persons with achylia gastrica, we may conclude that a radical physiological delinquency is present in the stomach, and that the stomach has functionally failed so far as its secretory work is concerned, but it still serves as a bag to halt the onrush of food and thus saves the jejunum and ileum from injury, and it also acts still as a mixer of the food. Furthermore this physiological failure of the stomach is of astonishingly little

significance so far as life is concerned because the food mass is chemically taken care of by the pancreatic, biliary and intestinal juices. To assume that achylia pancreatica always is associated with achylia gastrica is not justifiable. To attribute achylia gastrica to gastritis is not any more in line with our knowledge than to regard the achylia as primary and the gastritis as due to invasion due to removal of the acid barrier. In fact, achylia is a function of age, and represents a secretory failure which seems to parallel other evidences of growing old, and is similar to graying hair. The tie-up between gastric anacidity and nutrition is not too clear: in the case of pernicious anemia the lack of the intrinsic factor is, as we know, of causal importance to the disease. But in other cases, how much harm does achylia do? Most people feel that gastrogenous diarrhea is a misconception, simply because the majority of persons with achylia never have it. Through good surgery on dogs and man, the entire stomach may be removed without greatly inconveniencing the whole body, and, strangely enough, without precipitating pernicious anemia as a rule. How then can we speak of "gastric failure" when we know that the stomach is so unimportant to the body? Technically it shows partial failure in achylia, but since achylia usually causes no interference with the body as a whole, the term *failure* has only a local, chemical and histological meaning.

J. Edward Johnson (1) uses the term, but he expands into other fields and relates nutritional failure, and assumes that achylia pancreatica accompanies achylia gastrica, and that infection is the cause of the achylia. He sees a lot of pellagra in his section of the world, and we know that achylia is common in this disease, but he knows that pellagra is regarded everywhere (except by some "die hards" in Tennessee and elsewhere) as a pure nutritional deficiency in niacin. While Johnson does not seem to make a very good case for the term "gastric failure", he calls attention to the importance of studying more carefully the secretory chemistry of our patients. He follows the current, growing tendency to insist upon high protein diets of good biological value and he attacks the clinical problems of indigestion and malnutrition from a safe wide-angled viewpoint. It should be stated, in connection with achylia, that the use of HCl and pepsin does not prevent the onset of pernicious anemia in those who are destined to contract the disease, although these agents admittedly at times give comfort for reasons not too plain.

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SOCIALIZED MEDICINE

THOUSANDS of systems of contract practice and voluntary sickness and hospital insurance plans, as well as systems of compulsory sickness insurance in other nations have been studied.

These studies have led to the following conclusions:

1. These systems of distribution of medical service do not increase the medical service and do not decrease the cost.

2. Preventive medicine is no further advanced in any of the countries with compulsory insurance plans than it is in the United States. In fact, it lags far behind in many cases.

3. Medical resources are nearly always wasted in unnecessary and superficial treatment of minor diseases.

4. A double standard of practice is developed giving one kind of care to one class of the public, and another kind of care to the people under sickness insurance.

5. Illness is prolonged rather than shortened.

6. Diagnosis and treatment of disease tends to become mechanical and superficial.

7. The system becomes a bureaucracy of the government with a vast number of employees whose efforts are then directed toward making these bureaucracies permanent, rather than furnishing the best available medical service.

8. The system does not actually give to the worker anything beyond what he pays for himself. His contribution is deducted from his wages as well as from increased taxation.

The above facts we all know and now is the time to do something about them.

Hundreds of Medical Societies throughout the land are making resolutions against the present un-American Wagner-Murray bill No. S 1161.

Talk and resolutions are all very well and have had their place, but now we must act to save the glorious progress of free medicine; the steady progress of scientific effort and freedom of individuals, not doctors alone, but all people who have trusted and confided in their family physicians.

I suggest that we set up now an educational program in the press all over the country to save America. Such a program could be financed by popular subscription in the profession or by assessment of all members. There are 39,000 of our members serving the colors; there are 108,000 physicians in private practice. \$500,000 would buy considerable space in the leading newspapers. The National Physicians' Committee or the American Medical Association could sponsor this program. Let us talk it over and get going.

Give the public the facts!

Give the planners Hell!

Give the Government back to the people!

James L. Wyatt, M.D., Pres.
Fort Wayne Medical Society

THE INCREASE OF PEPTIC ULCER IN 20 YEARS

THE recent study by Tidy (1), whose article is digested elsewhere in this issue, indicates that in the last world war only 709 soldiers were discharged from the British Army because of "inflammation and ulceration of the stomach" and that, in the present war up till December, 1941, the number discharged because of peptic ulcer was 23,574. Tidy then shows by a study of case histories that the cases found in the army are largely persons who first acquired peptic ulcer in

civilian life before entering the Service. These findings mean that army service, in itself, is not any more provocative of peptic ulcer than civil life and, further, that during the past two decades there has been an inordinate increase in the incidence of peptic ulcer among civilians. Can this be due to better and more accurate diagnosis through greater use of X-ray facilities? Probably not, especially in a disease where the symptoms are as suggestive as they are in ulcer and where, too, there probably has been little increase in X-ray diagnosis in civil life among the middle and lower classes in Britain.

What are the factors of current civilization which, during the past 20 years, has occasioned so marked an increase in peptic ulcer in the civil population? Probably no one knows for sure. There is the possibility of nutritional causes, although as yet nothing startling has been revealed from this angle. Those who believe in the nervous causation of ulcer receive a cue from these figures to wax eloquent on the effects of current civilization on the individual psyche. Some will blame the increased use of tobacco. Many will justifiably confess that they do not know the factors responsible. However, preponderance of opinion among gastroenterologists just now favors a nervous origin of ulcer, as perhaps the chief cause of the lesions, and the work of the psychosomatic group is at least highly suggestive that such a cause exists, in most of the cases analyzed.

In Britain and America during the past 20 years society has undergone more or less marked organic changes. The trend toward socialization is the chief internal change, while the unsettled international conditions are reflected daily in the papers and radio programs to the extent of producing a "chronic crisis." The war between labor and capital both here and in Britain has been a constant source of tension since 1918. The financial depression of 1929-32 seemed to produce more individual tension in America than any factor in living

memory. The essential instability of American individual life is reflected plainly in the marked increase of divorce. In the realms of science and philosophy, there has been an abandonment of mechanistic theory, yet without the discovery of any suitable cosmology to take its place.

The majority of people, however, are indifferent to philosophical trends. Fear and frustration are the great, if incalculable, factors in the development of tension. Just work, and too much of it,—this seems to be operative right now during the war economy, in the causation of ulcer, and is seen chiefly among executives and department heads of large war industries.

The social metabolism has been stepped up greatly in the past two decades. Men and businesses succeed and fail faster. Wealth is largely syphoned into channels that concern a planned society. Individuals spend more time making personal profit, creating an estate and accounting their taxes. The simple idea of happiness, though mentioned in the preamble to the Constitution, has been completely neglected. The individual has been forgotten in the growing emphasis upon the State. The forgotten man is the man under everybody's hat, for he has psychologically overlooked himself. Visual and auditory stimulation have been increased by radio and the movies. Our spare time is commercialized, so that rest is a forgotten art. Propaganda, both political and advertising, whatever their merits, occupy time. Society through a habit of unconscious echopraxis, has become painfully standardized and the majority of people have become obligatory extroverts. In this tremendous world-revolution we must all reflect the deep tension which permeates a truly fearful and frustrated society.

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Book Reviews

Treatment of Experimental Data. By Archie G. Worthing and Joseph Geffner. New York, John Wiley and Sons Ltd., 342 pp., 1913 (\$4.00).

This is a book intended primarily for the physicist, chemist and engineer. It treats with the methods of mathematical and graphic representation of experimental data and requires a greater knowledge of mathematics than the average medical man possesses. However, it may prove of some use to certain experimental

physiologists who are engaged in quantitative measurements of bodily functions. The first three chapters are probably the ones which will be of most interest. These discuss thoroughly the various methods used in the representation of data by tables, graphs and mathematical equations. Chapter four has an excellent section on the methods which may be employed in determining the areas formed by irregular figures. The remaining chapters are chiefly of interest to the physicist and engineer.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

DEAKINS, M. AND TOOMY, J.: *Effect of pregnancy on the mineral content of dentin of human teeth.* (*Am. J. Obst. Gyn.*, V. 46, P. 265, 1943.)

The specific gravity of dentin was taken as an index of the degree of its calcification. In non-pregnant women this was found to be 2.08 while in pregnant women it was 2.12 (averages). The insignificant differences led the authors to conclude that calcium salts are not withdrawn from the dentin during pregnancy. They believe that the caries already present in pregnancy can not be attributed to demineralization of the dentin.—D. A. Wachen.

LOURIES, R. S.: *Rate of secretion of parotid gland in normal children: Measurement of function of autonomic nervous system.* (*Am. J. Dis. Child.*, V. 65, P. 455, March, 1943.)

After presenting the historical background of the problem concerning the mechanism, secretion, and function of the parotid glands, the author goes into considerable detail to describe the apparatus and the technique used in his study of the parotid activity. He then makes a general survey of the innervation of the parotid glands, and of the chief conditions affecting the activity. The author concludes by giving the results obtained in his study. Fifty-one children ranging from 3 to 14 years of age were selected and divided into nine age groups. The younger age groups, 3 to 5 years, showed the highest parotid salivary rate. From 5 to 7 years the rates were much lower, being one-half to one-fourth that of the earlier groups. From 7 to 14 there was a gradual slight drop to levels which approached in early puberty those of normal adults. The theory of developing inhibitory cortical activity is given some consideration as a possible factor causing

this drop. This study also pointed toward the existence of a "salivolacrimal reflex." The use of salivary rate as an aid in the localization of lesions of the brain in organic neurologic disorders, its use in differential diagnosis of types of hyperkinetic children and finally, its value in the field of mental deficiency are given consideration.—C. Foderaro.

WOODWARD, F. D.: *Carcinoma of the oesophagus.* (*South Med. J.*, V. 36, P. 590, August, 1943.)

The pertinent facts relative to carcinoma of the esophagus are pointed out. Most of them occur in men in the 4th and 5th decades. It is four or five times more frequent in men than in women, and occurs most frequently in the lower third in men and in the upper third in women. The majority are squamous cell in origin. When adenocarcinoma occurs, it is found in the lower and upper portions since these are the gland bearing portions. A not infrequent complication is tracheobronchial fistula. Metastases occur in 25-50%. A fairly early sign is dysphagia. When persistent, it must be regarded with suspicion. Bleeding may be present early if there is ulceration. Pain is usually substernal, but may be in the back. The diagnosis is made in the majority of cases by X-rays. Esophagoscopy is also of value, especially for obtaining specimens for biopsy. Radiotherapy and implantation of radium or radon have not been of much value as a means of therapy. Surgical removal and reconstruction of the esophagus offer most hope in these cases.—H. N. Metzger.

ALLISON, P. R.: *Carcinoma of the oesophagus treated by excision and reconstruction of ante-thoracic oesophagus.* (*Proc. Royal Soc. Med.*, V. 36, P. 341, May, 1943.)

A brief report on the method of excision of carcinoma

of the esophagus and its reconstruction is described. This is carried out in two stages. In the first stage, a loop of jejunum was anastomosed to the posterior aspect of the stomach, and the other end of the loop brought through a stab wound in the abdominal wall just below the costal margin. The continuity of the jejunum was restored and a jejunostomy performed. In the second stage, the esophagus was mobilized through the left thoracic route, and the growth removed through an incision at the base of the neck on the left side. The esophagus was then threaded through a tunnel in the subcutaneous tissue of the chest wall. A series of plastic operations was performed to make a new esophagus from the skin of the anterior chest wall. This was anastomosed above to the esophagus and below to the upper end of the isolated jejunal loop.—H. N. Metzger.

STOMACH

Pain in gastric disease. (Deutsch. Med. Wochenschr., V. 68, P. 628, 1942.)

The complexity of the problem of pain in gastric lesions is discussed. Pain is related more to the personality type than to the degree of pathologic change in the stomach wall. Late appearance of pain in gastric carcinoma is also discussed.—Courtesy Biological Abstracts.

BRAITHWAITE, L. R.: The role of bile in duodenal regurgitation. (Brit. J. Surg., V. 31, P. 3, 1943.)

The ancient and modern history of man's reaction to bile is discussed. The experiments of Beaumont on St. Martin are quoted. The conditions necessary for regurgitation into the stomach are a higher intraduodenal pressure or pressure gradient sufficient to open the pylorus if it is closed. Bile is not distressing to the stomach as has been thought, but is actually soothing and beneficial in vomiting. Bile is often found in the stomach at or near the end of the digestive period. Bile in the stomach may be important for healing of a peptic ulcer, but this effect is limited because bile does not often get past a spastic pylorus. The author states his independent experiences with cholecystgastrostomy, and quotes the work of Wayne Baheock, who also used this method to control gastric acidity and recommended it. The author feels that results might have been better and more lasting if the anastomosis would remain open; however it closed in about 50 per cent of the cases in 1½ to 2 years.—Wm. D. Beamer.

VOROBIOFF, SALOMON: Fractional gastric analyses. (Rev. Med. Rosario., V. 33, P. 194, 1943.)

Choice of the tests of gastric secretion is briefly discussed. The histamine test is compared with test meals and caffeine, and acidograms of the response to peptone and to histamine are presented.—Courtesy Biological Abstracts.

VIRASORO, J. E. AND MONSOLIC, R.: Nictalnic acid and habitual vomiting. (Pres. Med. Argentina, V. 30, P. 202, 1943.)

Nicotinic acid, given to infants in dosage of 15 mg. per kilogram of body weight, 2 or 3 times daily, im-

proves gastric tone, accelerates peristalsis, and favors gastric evacuation. This property of the drug proved useful in treating habitual vomiting of nursing infants, and in those with gastric atonia. There was no evidence of toxicity in those dosages employed.—Courtesy Biological Abstracts.

STOUT, A. P.: Pathology of carcinoma of the stomach. (Arch. Surg., V. 46, P. 807, June, 1943.)

The author presents a discussion of the pathology of carcinoma of the stomach with special reference to those phases of importance in diagnosis and treatment. The material was obtained from resected gastric carcinomas and autopsies. It is stated that the precancerous stomach is a much confused subject at present but he believes there is a definite relationship of cancer to chronic peptic ulcers of the stomach and to adenomatous polyps. The relationship to chronically inflamed mucous membranes may be important when there is a disappearance of the parietal and chief cells and replacement by mucus cells. Almost all are derived from the mucous secreting cells of the stomach. The histological picture varies from well differentiated to anaplastic cell types but the author feels little prognostic significance can be attached to this classification. With the cellular proliferation there is always a fibrinous framework formed, varying in amount with more being formed when the gastric wall is penetrated. Changes are also seen in the gastric mucosa. The gross types of gastric carcinoma are discussed as: fungating, ulcerated, spreading and no special type. The fungating tumors are usually well differentiated, project into the lumen, do not tend to become extensively ulcerated, and metastasize slowly. The ulcerated carcinomas are divided, on the basis of gross and histological pictures, into: primary ulcerated, secondary ulcerated, those forming on the margins of peptic ulcers and ulcers of superficial spreading and deep penetrating cancers. The spreading cancers are the superficial spreading form in the mucosa and the well known linitis plastica. The spread of gastric carcinoma is by contiguity, hematogenous and lymphogenous routes. Other lesions of the stomach that simulate carcinoma of the stomach are peptic ulcer, vitamin deficiency, gastritis, hypertrophy of the pyloric muscle in adults and not associated with tumors, syphilis, lymphosarcoma, smooth muscle tumors, and benign adenomatous polyps. In summarizing, the author has briefly discussed the precancerous stomach, the gross and histological pictures of gastric carcinoma, its spread and other lesions which may simulate it.—Robert J. Revelli.

BOWEL

GREENBLUM, M.: The significance of the Widal reaction in enteric diseases of children. (J. Pediat., V. 23, P. 150, August, 1943.)

Many physicians, who treat children, resort to the Widal test in attempting to diagnose illness which apparently are cases of typhoid fever. This sort of test should not be depended upon for a diagnosis of typhoid or paratyphoid fever. Bacteriological examination of the feces or blood should also be made.

Four cases are cited in which typhoid fever was suspected. In each instance a member of the Salmonella group (other than typhoid) was isolated. In order to make this clear the antigenic structure of the Salmonella group and the typhoid bacillus was reviewed, presenting their serological relationships.

It is important to determine the causative organism because of (1) clinical differences in the course of an infection and (2) public health problems in supervising carriers.—George P. Blundell.

BROWN, R. K.: *Sliding or paraperitoneal hernia of the pelvic colon.* (Surg. Gyn. Obst., V. 76, P. 91, 1943.)

Paraperitoneal hernia is difficult to repair and frequently tends to return. Brown shows that the sac of the sliding hernia is the mesentery of the pelvic colon turned inside out. Reconstruction of the mesentery after retraction of the bowel is possible if the opening into the abdominal cavity is made higher than is the usual practice. The higher opening permits better cleaning of the inguinal canal and the inner surface can be inspected.—N. N. Underhill.

FALKNER, R. L. AND WEIR, W. C.: *Left-sided pelvic lesions subsequent to appendicitis.* (Am. J. Obst. Gyn., V. 45, P. 874, 1943.)

Appendicitis as the cause of left-sided pelvic lesions should be considered when the subject is a young woman. The authors present three cases of such lesions. Two had a tubo-ovarian abscess and one a tubo-ovarian cyst; these apparently developed long after primary attacks of appendicitis.—N. N. Underhill.

GOODMAN, M. AND SILVERMAN, I.: *Acute appendicitis in patient with common contagious diseases.* (New Eng. J. Med., V. 228, P. 533, 1943.)

The records of patients admitted for contagious diseases between 1935 and 1941 were reviewed for the concomitant incidence of acute appendicitis. In a high percentage of these cases, the appendix was already gangrenous or ruptured. This may be attributed to the presence of the rash or other evidence of the contagious disease that tend to deflect the physician's attention from the abdomen. Over a ten year period there was an incidence of 0.23 percent among more than 15,000 cases of measles. Males predominate. It usually occurs in the preeruptive and early eruptive stage. The white cell count is the same as in cases uncomplicated by measles. The treatment is the same as for appendicitis under any other circumstance. The possibility that the appendicitis is due to the filterable virus which causes measles suggests itself. Appendicitis occurs very rarely in varicella, the authors reporting an incidence of only 0.12 percent in 3576 admissions. In fact, there is an extremely low incidence of appendicitis in all the common contagious diseases.—H. N. Metzger.

FARREL, J. T.: *Deformities of the duodenum other than those due to ulcer.* (Pennsylvania Med. J., V. 46, P. 1149, August, 1943.)

In this article the author clarifies the deformities of the duodenum by classifying and suggesting means for distinguishing between the various deformities.

The author classifies them according to their cause—congenital, inflammatory and extrinsic. Among those he includes are veils, diverticulum, duodenal redundancy, duodenitis, adhesions, foreign body, polyp, new growth, and extraduodenal pressure from the gall bladder or from pancreatic or intestinal tumors.

The means for distinguishing between these deformities is chiefly through radiological technique, toward which he makes a number of suggestions.—E. Glenn Clements.

YEOMANS, F. C.: *Stricture of the rectum.* (J. Med. Soc. N. J., V. 40, P. 222, June 1943.)

The recognition of lymphogranuloma venereum as the chief etiological factor in inflammatory stricture has aroused new interest in stricture of the rectum. The stricture may be congenital or traumatic but usually is the result of infection. Congenital anomalies of the terminal colon are rare. An emergency operation, such as colostomy, may tide the patient over from the time of discovery of the anomaly (after birth) to a time when permanent corrective procedure can be instituted (months or years later). Traumatic stricture may follow ulceration and infection from a foreign body, perforation, injections, instrumentation, operation, hemorrhoids, etc. Ulceration from radium application rarely leads to stricture. Inflammatory strictures make up the majority of cases; these result from simple non-specific infection by B. coli, streptococci, staphylococci, etc. Specific acute and chronic infections may also be a cause. Amebic and bacillary dysentery and gonorrheal proctitis are examples of the acute infections while syphilis, tuberculosis, actinomycosis and lymphogranuloma venereum are examples of the chronic.

Yeomans had 119 cases of stricture of the rectum. Of these, 8 were congenital, 15 traumatic (including post-operative), 9 secondary to fistula and 87 inflammatory. He reviews the characteristic symptoms, diagnosis and prognosis. Treatment is preventative, palliative and operative.—N. N. Underhill.

PANCREAS

CORNER, B. D.: *Primary carcinoma of the pancreas in an infant aged seven months.* (Arch. Dis. Child., V. 18, P. 106, June 1943.)

The author has searched the literature and concludes that primary malignant disease of the pancreas in infancy and early childhood is rare. The commonest features are cachexia, anorexia, digestive disturbances of various sorts, jaundice and the palpable tumor in the abdomen. In about twenty per cent of the cases glycosuria is also present.

The case reported by Corner is that of a seven-months old female with carcinoma of the pancreas which originated there. This is the second case reported in a patient under two years of age. Wasting was absent. The appetite was good. Marked features were a severe anemia, the abdominal tumor, and glycosuria. No biliary obstruction. —N. N. Underhill.

LIVER AND GALL BLADDER

COLVIN, MERL G.: *Hyperchromic anemia in chronic biliary dysfunction: response to liver therapy.* (*Pennsylvania Med. J.*, V. 46, P. 1168, August, 1943.)

The author noted in several biliary cases with anemia that treatment of the anemia with liver extracts not only improved the anemia but also the cholecystitis. Since biliary anemia has long been observed in cases with chronic cholecystitis, and since gall bladder disease is present rather frequently in pernicious anemia, he continued therapy for the anemia on similar cases and gradually evolved a concept relating the gall bladder syndrome to early pernicious anemia. This concept helps explain the confusion between the chronic gall-bladder syndrome and that of early pernicious anemia. The unexpected relief of the chronic digestive symptoms suggests that liver also contains a factor which improves the functional disturbance of the biliary system.—C. Glenn Clements.

OTTENBERG, R., AND SPIEGAL, R.: *The present status of non-obstructive jaundice due to infectious and chemical agents. Causative agents, pathogenesis, interrelationships, clinical characteristics. Sulfonamides.* (*Medicine*, V. 22, P. 27, 1943.)

Jaundice complicating treatment with sulfanilamide, sulfapyridine, and sulfathiazole is more common than with arsphenamine or cinchophens. The jaundice occurs as a result of the following mechanisms: (1) hemolytic anemia; (2) hepatic degeneration (most frequently); (3) rarely a combination of the preceding types. (1) Acute hemolytic (hemoglobinuric) anemia from sulfonamide compounds is a rare but distinctive entity and with great regularity it comes on within four days from the beginning of drug administration. It sometimes occurs after very small doses with no prodromata. The patient suddenly complains of severe general pains, especially of deep lumbar pain. He may be nauseated and occasionally vomits blood. The fall in hemoglobin occurs within several hours and may be as extensive as from 100% to 30% in 24 hours. The worst cases present the picture of severe shock. (2) The most common type of jaundice, that due to liver injury alone, does not appear promptly after a small dose as does acute hemolytic anemia, but generally after the drug has been taken for a week or two. Also it has appeared a week or more after chemotherapy had been terminated. Previous liver damage may predispose to acute hepatitis following sulfonamide therapy. Jaundice is more common in toxic patients. (3) The third variation of jaundice precipitated by the sulfonamides is represented by the cases with jaundice followed shortly by acute hemolytic anemia. So far only two cases have been reported.—E. Huene. (Biological Abstracts.)

TÖPPNER, RUDOLPH: *Visualization of the gall-bladder reflex by cholecystography.* (*Dtsch. Med. Wochenschr.*, V. 68, P. 1009, 1942.)

For X-ray visualization of the gallbladder reflex by means of biliselektan, injection of pituitary extract is not a suitable substitute for an egg yolk meal, but the latter is difficult to obtain. A small amount of freshly

fried potatoes, 100 grams fried in 10 grams of fat, regularly reduces contraction 45 minutes after ingestion.—Courtesy Biological Abstract.

HERBERT, F. K.: *Prothrombin deficiency in biliary obstruction and diseases of liver.* (*New Eng. J. Med.* V. 229, P. 265, Aug. 1943.)

Given sufficient vitamin K, the factor of its absorption determines the prothrombin level in plasma. Normal plasma prothrombin levels before biliary tract operations do not necessarily indicate a high safety margin. Operative procedures on the biliary tract usually result in a fall of plasma prothrombin and unless the prothrombin is restored, hemorrhages may occur several days after the operation. Restoration of plasma prothrombin was not successful in cases where liver cell injury existed. The author determined plasma prothrombin in 51 cases of obstructive jaundice with serum bilirubin values of 2.4 mg. per cent or higher. Hypoprothrombinemia was found in 68 per cent of the cases. Low plasma prothrombin was found in cases with very mild jaundice.—G. Klenner.

HICKEN, N. F. AND CORAY, O. B.: *Perforating gall-bladder: report of 24 cases.* (*Rocky Mountain Med. J.*, V. 40, P. 524, Aug. 1943.)

The authors report that complications were found in one quarter of all the cases of acute cholecystitis they had seen. They believe that acute cholecystitis is a problem for surgery and that corrective operation should be performed as soon as possible. From 12 to 24 hours are enough to prepare the patient for operation. Spinal anesthesia is advocated. Cholecystectomy should be performed whenever possible. Proper postoperative care is very important. A mortality rate of 9 per cent is reported. The damages of the acute stage could be prevented if operation were performed in cholecystitis cases during the chronic stage.—D. A. Wochen.

PERLE, W. J.: *Three gallbladders.* (*Virginia Med. Monthly*, V. 70, P. 331, July, 1943.)

This paper shows the stages taking place when large gall stones are spontaneously passed. Small stones admittedly pass through the common bile duct and out the bowel, but large stones present a different problem. The author cites three cases that point out how nature seemingly solves the problem.

The first case showed on operation a gall bladder firmly adherent on its lower half to the duodenum by a very broad adhesion. The second case showed a gall bladder attached opposite its upper third to the duodenum by an area of dense adhesions. A gall stone was found tightly imbedded in the area of adhesions, and was apparently eroding a path through the wall. It was removed by forceps, and an artificial fistula was made at the point, thus completing a cholecystenterostomy which nature was endeavoring to perform. The patient recovered fully. A third case seen at autopsy showed a large gall stone 2¼ cm. in diameter which obstructed the ileum completely. Upon opening the gall bladder, a fistula was found which penetrated the wall. A probe could be readily passed from gall bladder to duodenum, the fistula measuring 1 cm. by 1½ cm.—C. G. Clements.

MOTILITY

FORSTER, FRANCIS M., HELM, JOHN D. AND INGLESFINGER, FRANZ J.: *The electric potentials of the human small intestine.* (*Amer. J. Physiol.*, V. 139, P. 433, July 1943.)

Forster, Helm and Inglesfinger studied the electric potentials of the human small intestine. Contact Ag-AgCl electrodes were used on the exteriorized mucosa of the ileum in a patient with an old ileostomy and in four unoperated patients. Solder disc electrodes attached to a Miller-Abbott tube were employed. Electric potentials were elicited and these were found to correlate with mechanical evidences of contraction of the intestine. The electric pattern consisted of fast initial spikes followed by long base-line shifts with superimposed intermediate activity.—F. M. Forster.

FELDBERG, W.: *Effects of iodoacetic acid, glyceraldehyde and phosphorylated compounds on the small intestine of the rabbit.* (*J. Physiol.*, 102, P. 108, June 1943.)

Glucose and pyruvate stimulate excised rabbit's intestine because they supply energy needed for normal tone and rhythmic activity. The present study investigates the role of iodoacetic acid and glyceraldehyde, agents influencing carbohydrate metabolism, when they change this stimulating action of glucose and pyruvate. Iodoacetic acid, even though washed out after a few minutes contact, may poison smooth muscle in such a way as to render it insensitive to the stimulating action of glucose, but not that of pyruvate although this latter action is somewhat depressed. Glyceraldehyde also inhibits the stimulating action of glucose. Pyruvate stimulation is depressed to much less degree. Glyceraldehyde inhibition for both glucose and pyruvate is gradually and completely reversible when washed out of the bath. A slow conversion of glyceraldehyde into lactic acid, which is not oxidized by smooth muscle, is suggested.

3-d-phosphoglyceric acid, glucose-1-phosphate, hexose-6-phosphate, and fructose-1, 6-diphosphate were unable to replace glucose or pyruvate in their stimulating action on the smooth muscle preparation of intestine.—M. J. Oppenheimer.

MAGGI, ALBERTO, AND NAGERA, JUAN M.: *Experiment on the effects of massage on the digestive functions.* (*Rev. Asoc. Med. Argentina*, V. 56, P. 650, 1942).

X-ray studies revealed that abdominal massage accelerates gastric emptying; effects on the intestine depended upon the type of treatment, for light friction and effleurage decreased while deep massage increased propulsion. Effects on gastric secretion were irregular. Reflex effects were relatively more important than the direct physical effects. Clinical aspects are discussed.—Biological Abstract.

PATHOLOGICAL CHEMISTRY

ROE, J. H. AND GOLDSTEIN, N. P.: *Studies on pancreatic function II. Effect of injury to pancreas or liver upon the amylase and lipase content of the blood.* (*J. Lab. Clin. Med.*, V. 28, P. 1334, Aug. 1943.)

Using their own method for the determination of blood lipidases, and the Somogyi method for amylase, the authors studied changes in the level of these enzymes in cats following: 1) Mecholyl stimulation with and without pancreatic duct ligation (there was marked increase of both enzyme groups); 2) Pancreatectomy with control of diabetes by insulin (there was post-operative decrease of both, followed by a return to normal); 3) liver poisoning by 1 cc. of chloroform in oil subcutaneously per kilo. of body weight, but without autopsy (there was a decrease of triolein and olive-oil splitting enzymes, and an increase of those enzymes splitting ethyl and benzyl butyrates and tributyrin). From these results the authors concluded respectively that 1) pancreatic enzymes in blood are increased by vagal stimulus and duct occlusion; 2) both enzyme types have an extra-pancreatic source; 3) the fat-splitting enzymes occur as both esterase and lipase in the blood.—B. C. Riggs.

GOUGH, NANCY: *Diet and cholesterol concentration in blood and bile.* (*Brit. Med. J.*, P. 390, Sept. 25, 1943).

This is the report of an investigation to check the common belief that the level of cholesterol in the blood and bile is influenced by the intake of cholesterol in the food. Effect on the blood cholesterol on diets which were in some instances high in cholesterol (2,170 mg/day), and in other instances low in cholesterol (300 mg/day) were measured and showed no effect in eight cases out of ten. Experiments on the absorption of a single dose, 5 mg. of crystalline cholesterol by mouth, showed no effect in raising either the free or the esterified blood cholesterol. Feeding the cholesterol with fat did not change the result. The effect of high and low cholesterol diets on the cholesterol content of the bile was carried out and showed no rise in cholesterol that was related to the diet.

These experiments indicate there is no support to the contention that foods rich in cholesterol should be prohibited in the diet of patients with cholecystitis and and cholelithiasis.—C. G. Clements.

METABOLISM AND NUTRITION

STEFF: *Vitamins in the treatment of diseases* (*Deutsch. med. Wochenschr.*, V. 68, P. 835, 1942).

This review notes the usual occurrence of multiple deficiencies, destruction and poor absorption in gastrointestinal diseases, various therapeutic applications, effect on natural resistance, and detoxifying actions of the vitamins versus various drugs.—(Courtesy Biological Abstract.)

ROSTANFER, H. H., KOCHAKIAN, C. D., AND MURLIN, J. R.: *Digestion of whole wheat and white breads in human stomach.* (*J. Nutr.*, V. 26, P. 123, Aug. 1943).

Gastric digestion of various breads was studied in six human subjects. Samples of gastric contents were obtained by means of the Rehfuess tube and analyzed. Digestion was greatly improved if a small amount of pantothenic acid was added (in the form of high vitamin yeast). High vitamin yeast increased greatly the digestibility of whole wheat bread, bringing it into the same range of digestibility as white bread. Gastric digestion of the protein of whole wheat bread is lower than of white bread and this is not due to lack of pepsin secretion. Possibly the addition of non-fat milk solids increases the gastric digestion of bread protein. The amount of whole wheat bread which is digested is sufficient to supply the needed protein and calories and this constitutes an economic saving of wheat.—G. Klenner.

ALBANESE, A. A. AND IRBY, V.: *Observations on the biological value of a mixture of essential amino acids.* (*Science*, **78**, P. 286, Sept. 24, 1943).

Four diets differing in composition of the nitrogenous moiety were tried on a series of young rats. Diet "EAA" supplied the nitrogen only from a mixture of essential amino acids. Diet "A" consisted of an enzymatic digest of casein. In diet "CTII" the nitrogen was furnished by an acid hydrolysate of casein fortified with cystine and tryptophane. In diet "C" the nitrogen was derived from unhydrolyzed casein. The food intake of all the animals was kept at the same level.

The animals whose diet was restricted to the essential amino acids alone (diet "EAA" lost weight steadily and showed the poorest condition of all. When changed to diet "A" or "CTH" they began to regain weight promptly. Nitrogen balance studies showed that despite loss in weight, the animals kept on the mixture of essential amino acids retained nitrogen. The authors emphasize that "in the growing animals nitrogen retention can not be taken as a criterion of adequate nutrition." They conclude that the inadequacy of essential amino acids alone to maintain weight is perhaps "due in part to toxic effects of unnatural forms of certain amino acids that can not be utilized."—M. H. F. Friedman.

STRAUMFJORD, J. V.: *Vitamin A: Its Effect on Acne.* (*N. W. Med.* **17**, 42, 8, PP. 219-225).

Acne is defined as chronic and recurrent papular and pustular lesions of the pilosebaceous follicle. Pathogenesis is poorly understood and treatment inadequate. Etiologically, the blame for the disease has been placed on almost every conceivable cause. Some regard the disease as disturbance of fat metabolism. Straumfjord accidentally noted the disappearance of associated acne while treating follicular hyperkeratosis with large doses of vitamin A over many months of time. Of 100 patients who took 100,000 units daily of vitamin A over periods of not less than six months and usually longer, 84 per cent were "cured," 14 per cent improved and 2 per cent were unimproved. 36 per cent became completely free from acne. The effect of vitamin A on acne becomes intelligible when it is borne in mind that hyperkeratinization of the follicle is the basic primary

lesion in acne. The response of follicular hyperkeratosis on the one hand, and acne on the other, to the administration of vitamin A suggests that their cause is the same, that both are cutaneous lesions of vitamin A deficiency.

MISCELLANEOUS

WRIGHT, A. A.: *Vomiting sickness in Jamaica.* (*Brit. Med. J.*, P. 392, Sept. 25, 1943).

During the fall and winter in Jamaica there is a condition known as "vomiting sickness." This is manifested by a "bad feeling" in the abdomen and epigastrium, anorexia, vomiting, restlessness without anxiety, dehydration, eyelids usually closed over contracted pupils (which dilate at terminal stage), rapid and sometimes full pulse, slight temperature increase, and unconsciousness. Either response to symptomatic treatment or death within a few hours ensues. Contributive causative factors are: (1) lack of nutritional and vitamin requirements, (2) exposure to (and shock from?) sudden variations in temperature, (3) toxemia from possible intestinal origin.—John J. Cox.

BOGGENTOSS, A. H. AND ROSENBERG, F.: *Visceral lesions associated with chronic infections (rheumatoid) arthritis.* (*Arch. Path.*, **17**, 35, P. 503, 1943).

Clinical records and necropsy data on 30 patients suffering from rheumatoid arthritis were reviewed with a view to determining the nature of the visceral lesions in patients suffering with this disease. Observations on the heart indicated that rheumatic cardiac disease was present in 16 patients (53 per cent) and cardiac lesions other than rheumatic in 8 (27 percent). The pulmonary diseases present among these patients included notably, bronchopneumonia, fibrous pleuritis, bronchiectasis, pulmonary embolism and fat embolism. The interrelation of these pulmonary diseases with the rheumatoid arthritis was reviewed. Study of the liver failed to reveal any characteristic lesion which could be ascribed to rheumatoid arthritis. A number of abnormalities noted included hypertrophy, atrophy, chronic passive congestion, fatty change, central necrosis, amyloid deposits, subacute yellow atrophy, healed military tuberculosis and the serous hepatitis of Rossle and Eppinger. The lymph nodes and spleen, though occasionally enlarged during life, were found to show only various nonspecific inflammatory and degenerative effects. These included proliferation of reticulo-endothelial tissues, degeneration of lymph follicles, amyloid deposits, suppurative lymphadenitis, hypertrophy (of the spleen) and chronic passive congestion. A striking result of this study was the finding of low grade nonspecific glomerulonephritis in 19 of the cases. The implications of this lesion were considered. Other renal lesions present among these patients included chronic or subacute interstitial nephritis, nonsuppurative pyelonephritis, amyloid degeneration, nephrolithiasis with acute pyelitis and dissecting aneurysm of the right renal artery. Various lesions, mainly of minor importance, were encountered in other organs. These were reviewed and catalogued.—The Authors.

The Effect of Atropine Sulfate, Morphine Sulfate, Pilocarpine Hydrochloride, Prostigmine Methylsulfate, Sodium Salt of Dehydrocholic Acid and Secretin on the Gastric and Duodenal Secretions of Normal Persons When Fasting*

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and

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THE effects of atropine sulfate, morphine sulfate, pilocarpine hydrochloride, prostigmine methylsulfate, sodium salt of dehydrocholic acid and secretin on the volume and pH of the gastric secretions, duodenal secretions (with gastric contents excluded from the duodenum) and gastric and duodenal secretions aspirated already mixed from the duodenal cavity have been observed for fasting normal persons. The observations were undertaken to determine: (1) the effects of these drugs on separate gastric and duodenal secretions about which previous investigators have not always reported similar results; (2) the effect of these drugs on the mixed gastric and duodenal secretions under conditions as nearly as possible like those obtaining in the duodenum of the fasting normal person and (3) the rationale of the use of some of these drugs in the treatment of duodenal ulcer.

METHODS

Three normal human beings who volunteered were employed for all the observations. These persons were a woman (subject 1) in good health, twenty-two years old, who weighed 115 pounds (52 kg.) on whom results of a histamine test showed maximal free hydrochloric acid of 70 units and a maximal total gastric acidity of 80 units (Topfer's method); a youth (subject 2) in good health, eighteen years old, who weighed 135 pounds (61 kg.), on whom results of a histamine test showed maximal free hydrochloric acid of 95 units and a maximal total gastric acidity of 100 units; and a woman (subject 3) in good health, twenty-five years old, who weighed 135 pounds (61 kg.), on whom results of a histamine test disclosed maximal free hydrochloric acid of 100 units and maximal total gastric acidity of 110 units. All three of these persons were accustomed to swallowing gastric or duodenal tubes. The observations were made in the morning, with the persons in the fasting state.

Two types of procedure were employed; in the first type the duodenal and gastric contents were aspirated

continuously and separately but simultaneously, care was taken by means of continuous aspiration through the gastric part of the tube that the gastric contents did not enter the duodenum. Thus, the duodenal contents consisted only of a mixture of bile, pancreatic secretion and secretion of the duodenal glands.

In the second type of procedure the gastric part of the tube was clamped, thus allowing the gastric contents to accumulate in the stomach or to be expelled into the duodenum, according to the motility of the stomach. Thus, the duodenal contents consisted of a mixture of gastric content, bile, pancreatic secretion and the secretion of the duodenal glands.

The method of separate aspiration of the gastric and duodenal contents is a modification of a procedure originally introduced by Lim, Matheson and Schlapp (1). The tube used in this investigation was similar to the one used by Agren and Lagerlof (2); it consisted of a flattened, double tube of rather stiff rubber with several intakes for gastric contents and several for duodenal contents; the latter were distributed over the terminal 8 inches (20 cm.) of tube. When separate suction on the gastric and duodenal portions of the tube obtained clear, acid gastric juice from the former and clear alkaline, bile-stained fluid from the latter, the tube invariably was in the proper position. The position was determined by roentgenogram for the first several observations on each person and also in this manner at the time of later observations if any doubt arose whether the position of the tube was correct. When the gastric contents were not removed by separate suction the tube was in the same position as when they were but the gastric lumen of the tube was clamped off for the duration of the observation.

An apparatus was devised by means of which successive small samples of duodenal content could be withdrawn into the glass electrode chamber at frequent intervals without interrupting the continuous aspiration for more than two or three seconds. Thus, the pH of one sample could be determined while the following sample was being collected in a separate receptacle. A negative pressure of 16 inches (40 cm.) of water was employed to remove both gastric and duodenal contents.

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Continuous aspiration was done for about forty minutes before readings were made for record, in order to obtain a "basal" level. The pH of the mixed duodenal contents (gastric, hepatic and duodenal secretion) and of the duodenal contents, from which gastric juice was excluded usually were determined at intervals of two minutes. The duodenal contents for each successive twenty-minute period were measured in cubic centimeters. In most instances, the pH also was determined on the hourly and the total three hour specimens. In most cases the period of observation lasted three hours after the drug had been administered. When the gastric content was aspirated separately, the volume and the values for pH were determined for successive twenty minute specimens and for the total hourly specimen.

The values for pH were determined by means of a glass electrode and an electrometer (Cameron pH meter).

OBSERVATIONS WHEN DRUGS WERE NOT ADMINISTERED

Gastric and duodenal contents aspirated separately.

—Six observations in which the gastric and duodenal contents were aspirated separately were carried out. Two observations were made concerning each of the three persons.

The volume of duodenal content for each twenty minute period is given in table 1. The mean twenty minute volume was 6 c.c. The pH of successive small samples of duodenal contents were plotted for each of the six observations. A typical curve is labeled "normal control" in figure 1. The values for pH of successive samples were found to exhibit relatively slight variations; they remained just on the alkaline side of neutrality; the range was from 7 to 7.8 for all experiments.

The values for pH of the hourly specimens of duodenal contents (table 1) were slightly higher than the values for duodenal contents immediately after removal because of loss of carbon dioxide in the one to three hours elapsing between removal of the samples and the time determinations were made. However, they were valid for purposes of comparison with other readings obtained under the same conditions.

TABLE I

The volumes of fractions obtained each twenty minutes and the pH of the hourly specimens of the duodenal contents (gastric contents excluded) of three normal fasting persons

Ob- serva- tion	Subject	Successive twenty minute fractions of duodenal contents volume in c.c.										pH of hourly specimens		
		1	2	3	4	5	6	7	8	9	Mean	1st	2nd	3rd
1	1	3	3	4	4	6	8	11	6	6	5.7	—	—	—
2		6	8	9	11	9	9	—	—	—	8.7	—	—	—
3	2	7	6	8	9	6	8	8	—	—	7.4	7.45	7.45	7.30
4		7	9	7	8	6	9	5	8	8	7.4	7.70	7.65	7.60
5	3	2	2	3	2	7	5	4	2	4	3.4	7.85	7.65	7.60
6		4	2	5	5	3	4	5	—	—	4.0	7.80	7.75	7.60
Mean		5	5	6	7	6	7	7	5	6	6.1	7.70	7.63	7.53

*The corresponding observation in tables 1, 2 and 3 represents the same observation, that is, tables 1, 2 and 3 consist of different types of data obtained during the same six observations

The gastric contents were considered acceptable in all observations when they were grossly free from bile.

The mean volume of gastric contents for an interval of twenty minutes for all three persons (table 2) amounted to 23 c.c. The mean values for pH of the hourly specimens of gastric contents varied from 1.50 to 1.70 (table 2).

TABLE 2

The volumes of fractions obtained in twenty minutes and the pH of the hourly specimens of the gastric contents (duodenal contents excluded) of normal fasting persons

Ob- serva- tion	Subject	Successive twenty minute fractions of gastric contents volume in c.c.										pH of hourly specimens		
		1	2	3	4	5	6	7	8	9	Mean	1st	2nd	3rd
1	1	9	10	8	11	8	12	12	20	16	12	—	—	—
2		6	10	19	17	10	8	—	—	—	12	—	—	—
3	2	43	32	30	40	26	34	29	—	—	33	2.05	1.85	1.70
4		42	49	34	28	37	46	35	25	41	37	1.75	1.55	1.50
5	3	19	25	30	32	25	17	24	30	26	25	1.50	1.25	1.45
6		27	19	21	26	16	20	21	—	—	21	1.50	1.35	1.35
Mean		24	24	24	26	20	23	24	25	28	23	1.70	1.50	1.50

The values for pH were determined on the mixtures of the corresponding hourly specimens of gastric and duodenal contents, and then on the total combined specimen (table 3). It is interesting to notice that values for pH of the mixed gastric and duodenal contents were found to be only about 0.25 higher than the values for gastric contents alone. This reflects the low buffering power of duodenal content when the gastric juice is excluded from the duodenum and the secretin mechanism is not stimulated.

TABLE 3

The pH of the corresponding hourly specimens and of the total combined specimens of duodenal and gastric contents collected separately and then artificially mixed

Ob- serva- tion	Sub- ject	pH of hourly specimens of combined duodenal and gastric contents			Total 2 to 3 hour specimen
		1st	2nd	3rd	
1	1	—	—	—	—
2		—	—	—	—
3	2	2.35	2.15	2.10	2.20
4		2.00	1.90	1.85	1.90
5	3	1.55	1.40	1.55	1.55
6		1.65	1.55	1.50	1.60
Mean		1.89	1.75	1.75	1.81

Mixed gastric and duodenal secretions aspirated from the duodenum.—Eight observations were made in which the mixed gastric and duodenal secretions were aspirated from the duodenum; each lasted at least three hours. The mean volume obtained in twenty minutes was rather constant in different observations concerning the same person but varied considerably among different persons (table 4). The mean twenty minute volume of mixed duodenal contents for the three persons was 29 c.c. The values for pH of successive small samples of the duodenal contents were plotted for each of the eight observations. The curve for one observation is reproduced in figure 2 (labeled normal "control"). The prominent features of this and the other curves of the mixed duodenal contents are the wide range of values for pH and the existence of an irregular but fairly characteristic pattern of variation of the pH values. The values for pH extended from those near neutrality to those in the

zone of free acidity, that is from about 7 to less than a pH 4.

TABLE 4

The volumes of the successive twenty minute fractions of duodenal contents (gastric contents not included) in normal fasting subjects

Ob- serva- tion	Sub- ject	Successive twenty minute fractions of duodenal contents, volume in c.c.										Mean volume for each subject
		1	2	3	4	5	6	7	8	9	Mean	
7	1	8	12	13	18	19	22	24	32	45	21	22
8	1	14	16	13	28	32	25	24	26	35	23	
9	1	42	21	56	28	25	36	8	24	85	37	
10	2	19	18	28	33	17	31	73	27	40	37	38
11	1	16	19	42	22	56	48	44	34	19	38	
12	1	12	6	39	3	48	25	14	22	53	26	
13	3	28	34	44	20	11	36	35	13	26	26	26
14	1	43	46	1	8	11	20	38	28	26	27	
Mean		21	20	18	20	26	33	31	28	39		29

The mean values for pH of the hourly specimens for each of the three successive hours were, respectively, 5.89, 5.43 and 4.88; that of the entire three hour specimens was 5.53 (table 5).

TABLE 5

The pH values of the hourly and total specimens of duodenal contents (gastric contents not included) in normal fasting subjects

Ob- serva- tion	Subject	Hourly fractions of duodenal contents, pH values			Total 3 hour specimen	Mean for each subject Total 3 hour specimen
		1st hour	2nd hour	3rd hour		
7	1	6.80	6.35	5.60	6.05	6.20
8	1	6.90	6.40	6.00	6.45	
9	1	6.35	4.30	4.85	5.40	
10	2	6.45	6.25	4.00	5.70	5.25
11	1	4.70	4.95	4.30	4.60	
12	1	5.70	4.80	4.75	5.00	
13	3	5.25	4.00	4.60	4.70	5.16
14	1	6.15	4.45	4.95	5.80	
Mean		5.89	5.43	4.88		5.53

The pH of the combined gastric and duodenal secretion when aspirated separately and then mixed averaged 1.81 for the total specimens from subjects 2 and 3 while the pH of the combined gastric and duodenal secretions which were already mixed on withdrawal averaged 5.20 for the total specimens from the same two subjects and 5.53 for all three subjects. The higher values for pH of the gastric and duodenal contents which were already mixed when withdrawn probably are due to a decrease in volume and possibly in the acidity of gastric juice brought about by entrance of gastric juice into the duodenum as suggested by the work of Day and Webster (3), of Griffiths (4) and of Shay, Ger-shon-Cohen and Fels (5) and to an increase in volume and alkalinity of duodenal contents brought about by entrance of acid gastric juice into the duodenum and by its effect on pancreatic juice through the secretin mechanism and on the flow of bile.

It is realized that the observations do not indicate quantitatively the relationship of volume and pH of the gastric and duodenal secretions of the fasting human being when the fluids are not being aspirated continuously. However, it is obvious that the method of continuous aspiration permits sufficient stimulation of the secretin mechanism by the acid gastric juice be-

tween the time of its entrance into, and removal from, the duodenal cavity to provide enough buffering material to raise the pH of the mixed gastric and duodenal contents from the low of 1.81 when mixed outside the stomach to a mean of 5.53. It is possible, and indeed probable, that a similar but more marked effect occurs under normal physiologic conditions. The pH of the duodenal contents obtained in this study were approximately the same as found in the observations of Miller and Karr (6) and of Kearney, Comfort and Osterberg in which continuous aspiration also was practiced.

OBSERVATIONS AFTER ADMINISTRATION OF VARIOUS DRUGS

Atropine sulfate was administered subcutaneously in doses of 1/100 grain (0.00065 gm.); morphine sulfate subcutaneously in doses of 1/6 grain (0.01 gm.); pilocarpine hydrochloride subcutaneously in doses of 1/10 grain (0.006 gm.); prostigmine methylsulfate subcutaneously in doses of 0.5 mg.; sodium salt of dehydrocholic acid intravenously in doses of 10 c.c. of a 20 per cent solution and secretin intravenously in doses of 1 clinical unit per kilogram of body weight. The number and duration of observations on the three subjects is given in table 6. Data of the same scope as those obtained in observations in which drugs were not given were secured after the administration of the several drugs and analyzed as in the preceding section but only the mean twenty minute volumes and mean values for pH of the hourly and of the total three hour specimens for each person as well as for all three persons are given in table 6.

Gastric secretion aspirated separately.—The mean volume of the gastric contents (23 c.c.) for intervals of twenty minutes obtained in observations in which drugs were not used, was decreased by administration of atropine sulfate to 5.3 c.c. and by morphine sulfate to 8 c.c.; it was not significantly changed by administration of sodium salt of dehydrocholic acid and was doubled as a result of a dose of pilocarpine hydrochloride and prostigmine methyl sulfate (table 6).

Comparison of the mean pH of the specimens collected during the first, second and third hourly periods in observations in which no drugs were given with the pH of similar specimens collected after administration of drugs (table 6) discloses that the pH of the gastric secretion was only slightly affected, if at all, by doses of prostigmine methyl sulfate and sodium salt of dehydrocholic acid but was increased by doses of atropine sulfate and pilocarpine hydrochloride.

Comment.—Previous investigations on the action of atropine sulfate on gastric secretion have given conflicting results (8, 9, 10). The results of Keefer and Bloomfield (11), Myerson and his co-workers (12), Winkelstein (13) and Immerman (14) indicated, however, that atropine sulfate depressed markedly the psychic and basal flow of gastric secretion. Our results clearly demonstrated that atropine sulfate in the dosage administered had a depressing effect on the gastric secretion of fasting persons and produced both marked reduction in volume and increase in the values for pH

of the gastric secretion. The full effect of atropine sulfate does not seem to have been reached until the third hour (table 6). Atropine sulfate depressed the secretion of acid so much that the pH in the third hour after its administration approached 4.0 or more which indicates that free acid is not present in the gastric contents. These changes, too, were accomplished in spite of a reduction of saliva secreted and swallowed.

Results of previous investigations on the action of morphine sulfate on gastric secretion also have been conflicting. The experimental studies with dogs by Reigel many years ago demonstrated that while a decrease in gastric secretion occurred in the first hour following the injection of morphine, secretion was stimulated subsequently (15). Kreuger concluded from the conflicting reports that morphine sulfate does not depress gastric secretion in man (16). Our findings, on the contrary, indicated that morphine sulfate definitely depressed the gastric secretion of a fasting person for a period of three hours.

Data not given in table 6 show that the increase in volume of gastric contents was limited to the first hour after the administration of pilocarpine hydrochloride as was the increase in pH. The salivation that occurred and the increased volume of saliva swallowed during this first hour may account for the changes noted. On the other hand, pilocarpine hydrochloride is said to cause a secretion of gastric juice with higher than usual pH (17). Our observations unfortunately do not clearly indicate the effect of pilocarpine hydrochloride on gastric secretion. On the contrary, data in table 6 indicate that prostigmine methylsulfate definitely increased the secretion of acid by the stomach; it increased the volume but not the pH of the gastric contents obtained during fasting. Salivation did not appear to be a factor, as the flow of saliva was increased only slightly if at all by prostigmine methylsulfate.

Duodenal contents (bile, pancreatic juice and secretion of duodenal mucosa) aspirated separately.—The mean volume of duodenal contents of 6 c.c. for twenty minute periods obtained in observations in which drugs were not given was decreased by doses of atropine sulfate to 3.3 c.c. and morphine sulfate to 2.5 c.c., was unchanged by pilocarpine hydrochloride (7.2 c.c.) and was increased by prostigmine methylsulfate to 13.5 c.c., by sodium salt of dehydrocholic acid to 17.5 c.c. and secretin to 38.3 c.c. (table 6).

The mean values for pH of the specimens collected during the first (7.73), second (7.63) and third (7.53) hours in observations in which no drugs were used were essentially unchanged by doses of atropine sulfate, pilocarpine hydrochloride, prostigmine methylsulfate and sodium salt of dehydrocholic acid. Comparison of curves constructed of the pH of successive small samples of duodenal contents obtained in observations in which drugs were not given with curves similarly constructed of the pH of successive small samples of duodenal contents obtained after stimulation with the several drugs revealed that doses of atropine sulfate, morphine sulfate, pilocarpine hydrochloride, prostigmine methylsulfate and sodium salt of

dehydrocholic acid did not affect the pH. Such a comparison does show, however, that secretin (fig. 1) markedly affected the pH; it elevated and maintained pH at more than 8 for long periods of time, as has been previously shown (18, 19).

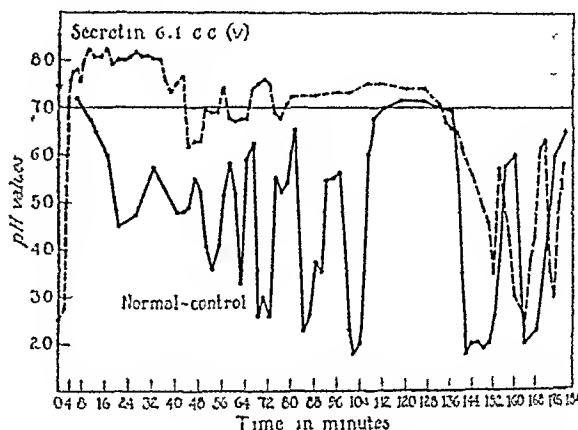


FIGURE 1.

Values for pH of the duodenal contents when the gastric contents were excluded from the duodenum in subject 2, when drugs were not given and after the administration of pilocarpine, sodium salt of dehydrocholic acid (Decholin) and secretin.

The diluting the neutralizing value of the duodenal contents therefore was not influenced by administration of pilocarpine hydrochloride, was decreased by atropine sulfate and morphine sulfate and increased by prostigmine methylsulfate, sodium salt of dehydrocholic acid and secretin. The diluting and neutralizing value of duodenal contents was increased more markedly by secretin than by prostigmine methylsulfate or sodium salt of dehydrocholic acid.

At the conclusion of each experiment the gastric contents and the duodenal contents were artificially mixed in a flask and the values obtained compared with values obtained in observations in which drugs were not given. The mean pH of 1.8 of the artificially combined total three hour specimens of gastric and duodenal contents obtained in observations in which drugs were not given was slightly lower than the mean pH of similar specimens after administration of pilocarpine hydrochloride, after prostigmine methylsulfate and after sodium salt of dehydrocholic acid and markedly lower than after administration of atropine sulfate (table 6). Sodium salt of dehydrocholic acid tripled the volume of duodenal contents yet it increased the mean pH of the artificially mixed duodenal and gastric contents only slightly over that found when drugs were not given; this observation reflected the low buffering power of bile. The marked effect of atropine sulfate reflected its marked depressing influence in gastric secretion.

Comment.—The reduction in volume of duodenal contents (gastric juice excluded) following administration of atropine sulfate may have been due to inhibition of secretory activity of the small intestine (20) and to relaxing effect on the gallbladder and bile ducts (21,22). While atropine sulfate reduces the flow of pancreatic secretion when gastric juice is not excluded from the duodenum (23,24), its effect on the

TABLE 6
Observations after administration of various drugs

Drugs administered	Sub- ject	Duodenal and gastric contents separately aspirated										Mixed gastric and duodenal contents aspirated from duodenum				
		Duodenal contents					Gastric contents					pH of combined gastric and duodenal specimens†	Duration, minutes	Number of observa- tions		
		pH of hourly specimens			Mean 20 min. vol., c.c.	Number of observa- tions	pH of hourly specimens			Mean 20 min. vol., c.c.						
		1st	2nd	3rd			1st	2nd	3rd							
None	1	—	—	—	7.2	2	—	—	—	12.0	—	—	22.0	2	6.20	
	2	—	7.63	7.55	7.45	2	—	—	—	35.0	—	—	38.0	3	6.23	
	3	—	7.83	7.70	7.60	2	—	—	—	23.0	—	—	26.0	3	5.16	
	Mean	180	7.73	7.63	7.53	—	—	—	—	23.0	—	—	29.0	—	5.53	
Atropine sulfate 1/100 grain (0.00065 gm.)	1	—	—	—	—	0	—	—	—	—	—	—	9.0	2	6.80	
	2	—	7.45	7.40	7.45	2	—	—	—	6.5	—	—	10.5	2	5.85	
	3	—	7.45	7.40	7.45	2	—	—	—	4.0	—	—	5.0	2	5.75	
	Mean	180	7.45	7.40	7.45	—	—	—	—	5.3	—	—	8.2	—	6.13	
Morphine sulfate 1/6 grain (0.01 gm.)	1	—	—	—	2.0	1	—	—	—	5.0	—	—	5.0	1	—	
	2	—	—	—	3.0	2	—	—	—	11.0	—	—	8.0	2	—	
	3	—	—	—	—	0	—	—	—	8.0	—	—	9.0	1	—	
	Mean	240	—	—	—	—	—	—	—	—	—	—	7.0	—	—	
Pilocarpine hydrochloride, 1/10 grain (0.006 gm.)	1	—	—	—	8.0	1	—	—	—	31.0	—	—	42.5	2	5.10	
	2	—	7.65	7.50	7.50	3	—	—	—	53.0	—	—	72.0	2	4.70	
	3	—	7.95	7.60	7.50	2	—	—	—	52.0	—	—	57.5	2	3.60	
	Mean	120	7.80	7.55	7.50	—	—	—	—	45.0	—	—	57.3	—	4.47	
Prostigmine methyl- sulfate, 0.5 mg.	1	—	—	—	13.5	1	—	—	—	21.0	—	—	47.0	2	6.20	
	2	—	7.45	7.50	7.40	2	—	—	—	71.0	—	—	77.0	2	6.35	
	3	—	7.45	7.40	7.45	2	—	—	—	44.0	—	—	44.0	2	6.20	
	Mean	120	7.45	7.45	7.43	—	—	—	—	45.0	—	—	56.0	—	6.25	
Sodium salt of dehydro- cholic acid 10 c.c. of 20 per cent solution	2	—	7.40	7.35	7.55	2	—	—	—	30.5	—	—	57.0	2	6.15	
	3	—	7.60	7.65	7.45	2	—	—	—	22.5	—	—	37.0	2	6.35	
	Mean	120	7.50	7.50	7.50	—	—	—	—	26.5	—	—	47.0	—	6.25	
	Secretin	1	—	—	—	—	0	—	—	—	—	—	—	54.0	1	7.65
	2	—	—	—	42.5	1	—	—	—	—	—	—	80.5	1	7.60	
	3	—	—	—	34.0	1	—	—	—	—	—	—	65.5	1	7.70	
	Mean	80	—	—	38.3	—	—	—	—	—	—	—	66.7	—	7.65†	
	Total	4,800											6,960			

*Duration after the administration of the drug and represents the period of time from which the mean twenty minute volume was obtained
†Volumes for combined duodenal and gastric specimens collected during the three hour period, except in observations with atropine sulfate in which the combined duodenal and gastric specimens were collected during the second and third hour after the administration of the drug.
‡Mean pH of the total two hour specimen. The mean pH of the total three hour specimen was 7.30 while the pH of the third hour specimen alone was 5.25.

secretion of pancreatic juice during fasting when the gastric juice is excluded from the duodenum has not been determined in man, so far as we could find out.

The observations using morphine sulfate need further description to record certain results not recorded above. In two observations in which morphine sulfate was given, the bile color of the duodenal content disappeared completely within twenty minutes after its administration. In a third observation the bile color progressively and markedly diminished in degree during the first forty minutes and then persisted as a light yellow solution for another forty minutes, after which only a faint yellowish tinge was noticeable. During one observation glyceryl trinitrate 1/100 grain (0.00065 gm.) was administered sublingually three hours after, and a pearl of amyl nitrite by inhalation three hours and forty minutes after administration of morphine sulfate, yet the bile color did not return until four hours and ten minutes had elapsed after administration of morphine sulfate. An ampule of amyl nitrite was inhaled by one subject at the end of the eighth twenty minute period of one observation but a flow of bile did not occur for another forty minutes. Similar observations were obtained using codeine sulfate and dilaudid hydrochloride. These observations indicated that these drugs prevented, or almost completely prevented, the entrance of bile into the duodenal cavity for about three to four hours after their administration and that administration of glyceryl trinitrate and amyl nitrite did not hasten the return of bile to the duodenal cavity.

These data did not indicate that pilocarpine hydrochloride altered the secretion of any of the components of the duodenal contents. On the contrary prostigmine methylsulfate appears to do so since the volume of the duodenal contents was increased, as previously reported (25). Since the pH of the duodenal contents was not significantly altered, it is probable that the increase in volume was not due to an increased flow of pancreatic juice of the secretin type.

The volume of duodenal contents was increased definitely by intravenous administration of sodium salt of dehydrocholic acid. The increases may be attributed to the increased flow of bile into the duodenum. However, the possibility that increased pancreatic secretion contributed to the increased volume must be entertained, since bile salts introduced into the intestine stimulate pancreatic secretion (26), containing bicarbonate in the concentrations seen after the intravenous administration of secretin (27). However, the increase in pH was so small that the volume of pancreatic juice entering the duodenum during stimulation with sodium salt of dehydrocholic acid must have been small.

Mixed duodenal and gastric secretions aspirated from duodenum.—The mean volume of mixed gastric and duodenal contents obtained at intervals of twenty minutes which was 29.0 c.c. for all observations on all three subjects when drugs were not given was decreased by doses of atropine sulfate to 8.2 c.c. and by morphine sulfate to 7.0 c.c., was doubled by doses of pilocarpine hydrochloride and prostigmine methyl-

sulfate, was increased about 50 per cent by sodium salt of dehydrocholic acid and was more than doubled by secretin (table 6).

The mean pH of mixed gastric and duodenal contents for the three hour period obtained in observations on all three subjects was lower after administration of pilocarpine hydrochloride (4.47), was slightly higher after atropine sulfate (6.13), prostigmine methylsulfate (6.25) and sodium salt of dehydrocholic acid (6.25) but was markedly higher (7.65) after administration of secretin (table 6) than in the observations in which drugs were not given (5.53).

The comparison of curves of the pH of successive small samples of mixed duodenal and gastric contents obtained when drugs were not given with those of pH of similar samples obtained after the different drugs were given yields interesting results. The action of atropine sulfate (fig. 2) resulted in a reduction in

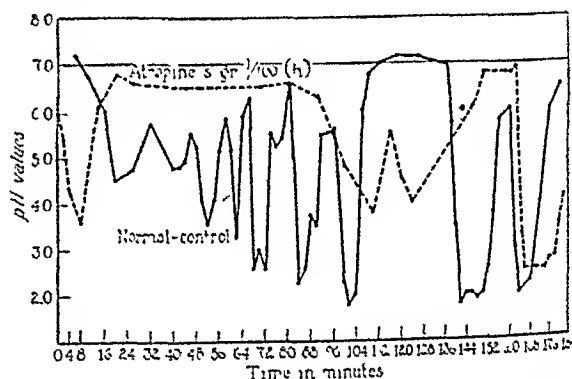


FIGURE 2.
Fluctuations in the pH of the duodenal contents when the gastric contents were allowed to enter the duodenum in subject H. A., when a drug was not given and after the administration of atropine sulfate.

range and frequency of fluctuation of pH and in elevation of the general level of the curve. The action of morphine sulfate reduced markedly the frequency of gastric emptying and the fluctuations in pH of the mixed gastric and duodenal contents. The action of pilocarpine hydrochloride (fig. 3) did not markedly

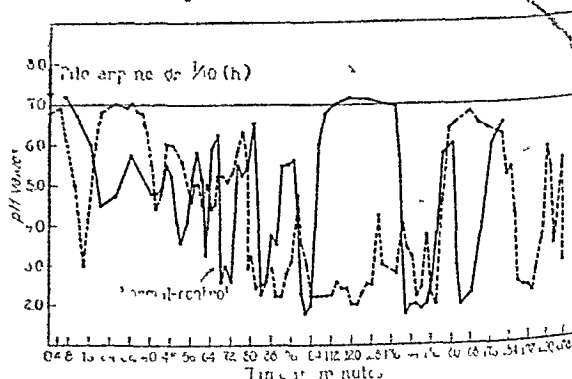


FIGURE 3.
Fluctuations in pH of the duodenal contents when the gastric contents were allowed to enter the duodenum in subject H. A., when a drug was not given and after the administration of pilocarpine hydrochloride (H.).

change the configuration of the curve during the first eighty minutes but produced a marked depression of values for pH from eighty to 160 minutes after its

administration and erased the characteristic fluctuations in the pH of the combined contents observed when drugs were not given. The mean values for pH were not much greater than those of acid gastric juice during the second eighty minute period. In all other observations after doses of pilocarpine except one the curves were similar to, and were as marked as that illustrated in figure 3. In the exception the pH rose more frequently to about 7.0, as in the observations in which no drugs were administered but it also reached lower levels and the duration of these low levels was much greater than in the observations in which drugs were not administered. The action of prostigmine methylsulfate produced more frequent and wider fluctuations of values for pH than occurred when the drugs were not given (fig. 4). The action of sodium

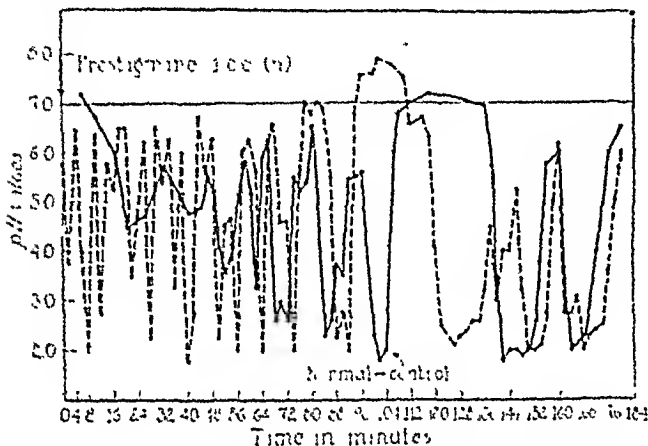


FIGURE 4.

Fluctuations in pH of the duodenal contents when the gastric contents were allowed to enter the duodenum in subject H. A., when a drug was not given and after the administration of prostigmine methylsulfate (H).

salt of dehydrocholic acid (fig. 5) elevated slightly the general level of values above those encountered when drugs were not given and the fluctuation in values was

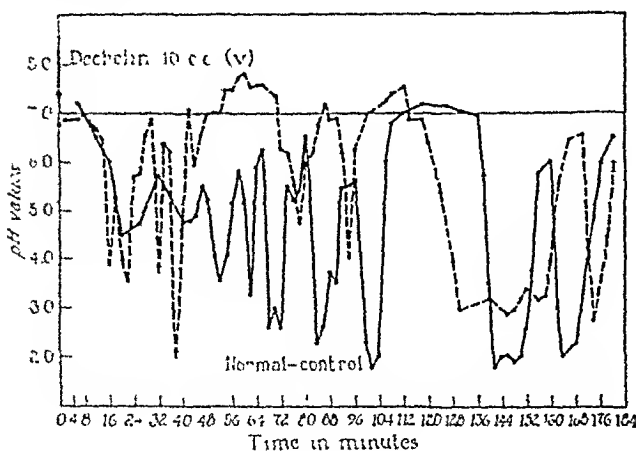
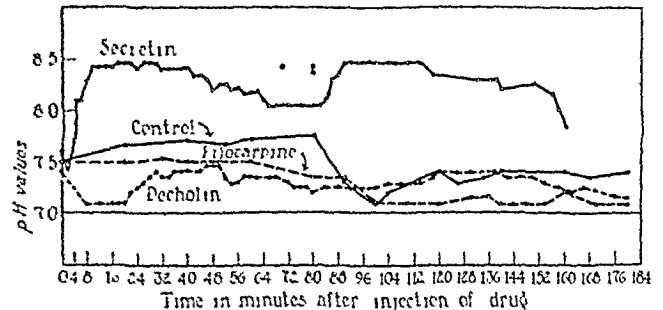


FIGURE 5.

Fluctuations in pH of the duodenal contents when the gastric contents were allowed to enter the duodenum in subject H. A., when a drug was not given and after the intravenous administration of sodium salt of dehydrocholic acid.

increased in frequency. The action of secretin was definite and marked (fig. 6). It elevated the pH above neutrality. The highest values were pH 8.20 in this observation (fig. 6) and 8.5 and 8.35 in the obser-

vations on the other two persons. The values remained at high level during the first two to three hours in spite of the entrance of some acid gastric material into the duodenal cavity.



- In the secretin experiment atropine sulphate gr $\frac{1}{160}$ (h) given at 70 minutes after onset of experiment
- In the secretin experiment a second injection of same dosage of secretin given 80 minutes after onset of experiment

FIGURE 6.

Fluctuations in pH of the duodenal contents when the gastric contents were allowed to enter the duodenum in subject H. A., when a drug was not given and after the intravenous administration of secretin.

COMMENT

Atropine sulfate reduced the volume and elevated the pH of the gastric and duodenal contents which were mixed before aspiration. Although quantitative measurements of the various effects of atropine sulfate on gastric and duodenal secretions which were mixed before aspiration have not been possible, it appears that its direct influence on duodenal secretions is of much smaller magnitude than its influence on gastric secretions. At least this was true in the observations in which the gastric and duodenal contents were aspirated separately. It also appears that the reduction in volume and increase in values for pH of the gastric secretions produced by atropine sulfate accounts for the major portion of the reduction in volume and elevation in pH of the mixed duodenal and gastric contents obtained under fasting conditions and that reduction in quantity and elevation in pH of gastric contents entering the duodenum is followed by increase in the mean pH of the duodenal contents (mixed gastric and duodenal secretions). This latter observation agrees with that of Kearney, Comfort and Osterberg (7), that the amount of acid gastric juice entering the duodenum seemingly does influence roughly the level of the pH of the duodenal contents of normal persons.

Certain observations in addition to those recorded concerning gastric and duodenal contents which were mixed before aspiration were made after doses of morphine sulfate. In all these observations the bile color of the mixed duodenal contents disappeared within twenty minutes and usually within the first ten minutes following administration of morphine sulfate. In one observation glyceryl trinitrate, 1/100 grain (0.0065 gm.) was administered sublingually every twenty minutes from the end of the first period of twenty minutes to the end of the seventh twenty minute period after administration of morphine sulfate. In addition, atropine sulfate was given intravenously

at the end of the sixth twenty minute period. In spite of the giving of glyceryl trinitrate and atropine sulfate the first fraction of duodenal contents to exhibit the color of bile was that collected during the ninth twenty minute period or in the second twenty minute period after the seventh dose of glyceryl trinitrate. In another observation, 10 c.c. of a saturated solution of magnesium sulfate was given by way of a duodenal tube. The suction was stopped for ten minutes and then as suction was resumed, morphine sulfate, 1/6 grain (0.01 gm.) was injected subcutaneously. Only during the first ten minutes after injection of morphine sulfate were the duodenal contents bile colored. Duodenal lavage with saturated solution of magnesium sulfate at the end of the fourth and sixth twenty minute periods did not evoke a flow of bile. Bile appeared in the duodenum 170 minutes after administration of morphine sulfate in this observation, which is only slightly earlier than in those observations in which magnesium sulfate was not administered. The results were similar to those obtained on the duodenal contents unmixed with gastric contents. Other observers have reported that morphine sulfate increases the tonus of the sphincter of Oddi with retardation of the flow of bile (Reach), (28) and reduces the secretion of bile when administered to dogs (29), that morphine sulfate contracts the lower end of the common bile duct and increases the intraductal pressure of patients whose gallbladders had been removed and a T tube inserted in the common bile duct (30, 31). Dilaudid and codeine had a similar effect. Our observations indicated that morphine also usually interrupted sharply and completely the flow of bile into the duodenal cavity of persons with intact biliary tracts and normally functioning gallbladders for a period of three to four hours, an effect which presumably is due to either constriction of the lower end of the common bile duct or to suppression of the flow of bile, or both. Codeine and dilaudid had a similar effect.

Glyceryl trinitrate, amyl nitrite, theophylline with ethylenediamine lowered the increased intraductal pressure produced by morphine sulfate in cases in which gallbladders have been removed and a T tube inserted into the common duct (30). It has been assumed that these drugs produced relaxation of the common bile duct and of the sphincter of Oddi which permitted flow of bile into the duodenum with a resultant fall in ductal pressure. Our observations did not indicate that glyceryl trinitrate or amyl nitrite had any such effect on persons whose biliary tracts were intact and healthy.

Prostigmine methyl-sulfate increased the diluting and neutralizing effect on the duodenal secretions more than the secretion of acid by the stomach, since the mean pH (6.25) of the three hour specimens of mixed duodenal and gastric contents after administration of prostigmine methyl-sulfate was greater than pH (5.53) of the three hour specimens obtained when no drug was given. Pilocarpine hydrochloride increased the secretion of acid by the stomach more than it increased the diluting and neutralizing power of the duodenal contents since mean pH 4.47 of the three hour specimens

was less than mean pH 5.53 of the three hour specimens obtained when no drugs were given.

Of all the drugs employed in these experiments, secretin produced the greatest increase in volume of the duodenal contents and was the only one which markedly increased the pH of the individual small samples of duodenal contents above the values obtained in observation in which drugs were not given, whether the duodenal contents were collected mixed or unmixed with gastric contents. The values for pH of the duodenal contents rose to 8.40 to 8.45 in observations in which gastric and duodenal secretions were aspirated separately and almost to the same level in those observations in which gastric contents were allowed to enter the duodenum and then aspirated mixed with the duodenal secretions. The increased flow of bile produced by the intravenous administration of sodium salt of dehydrocholic acid serves to increase the pH of duodenal contents but this increase is much less than that produced by secretin.

SUMMARY AND CONCLUSIONS

The method of continuous aspiration of gastric and duodenal contents has been applied in the study of volume and pH of the gastric and duodenal contents.

The volume and pH of the gastric and duodenal contents have been determined without and after the administration of atropine sulfate (1/100 grain or 0.00065 gm., subcutaneously), morphine sulfate (1/6 grain, or 0.01 gm., subcutaneously), pilocarpine hydrochloride (1/10 grain, or 0.006 gm., subcutaneously), prostigmine methyl-sulfate (1 mg. subcutaneously), sodium salt of dehydrocholic acid (10 c.c. of a 20 per cent solution intravenously) and secretin (1 clinical unit per kilogram of body weight, intravenously). Two types of observation were carried out. In the first type of observation the gastric and duodenal contents were aspirated simultaneously but separately; in the second type the gastric contents were allowed to enter the duodenal cavity and the mixed gastric and duodenal contents were aspirated.

In observations in which gastric and duodenal contents were aspirated separately and no drugs were given, the mean volumes of duodenal and gastric contents for twenty minute periods were, respectively, 61 and 23 c.c. The mean pH of duodenal contents was 7.6 and of gastric contents 1.6 in the same type of observations.

In observations in which gastric contents were allowed to enter the duodenum and the mixed gastric and duodenal contents were aspirated and no drugs were given, the mean volume of the duodenal contents for periods of twenty minutes was 29 c.c. and the mean pH of the duodenal contents 5.53. In spite of continuous aspiration of the duodenal contents, the acid gastric juice apparently remained in the duodenal cavity long enough to stimulate the hormonal mechanism controlling the secretion of bile and pancreatic juice and raise the mean pH values of the gastric contents to levels well above those (1.41) found when the duodenal and gastric contents are aspirated separately and then mixed.

In observations in which the gastric and duodenal contents were aspirated simultaneously but separately, the volume of gastric contents was markedly decreased by both atropine sulfate and morphine sulfate, was apparently unaffected by sodium salt of dehydrocholic acid but was increased both by pilocarpine hydrochloride and prostigmine methylsulfate. The pH of the gastric contents were elevated by atropine sulfate, by pilocarpine hydrochloride during the first hour after stimulation and were unaffected significantly by prostigmine methylsulfate and sodium salt of dehydrocholic acid.

In the observations in which the gastric and duodenal contents were aspirated simultaneously but separately, the volume of duodenal contents was decreased by both atropine sulfate and morphine sulfate, was practically unchanged by pilocarpine hydrochloride and was increased by prostigmine methylsulfate, sodium salt of dehydrocholic acid and secretin; the pH of the duodenal contents was unchanged by atropine sulfate, pilocarpine hydrochloride, prostigmine methylsulfate and sodium salt of dehydrocholic acid, but was increased by secretin.

In observations after drugs were given in which the gastric contents were allowed to enter the duodenum and the mixed gastric and duodenal contents then were aspirated, the volume was decreased by atropine sulfate and morphine sulfate and increased by pilocarpine hydrochloride, prostigmine methylsulfate, sodium salt of dehydrocholic acid and secretin; the mean values for pH were lowered slightly by pilocarpine hydrochloride and were elevated slightly by atropine sulfate, prostigmine methylsulfate, sodium salt of dehydrocholic acid and markedly by secretin.

Atropine sulfate reduced both the amount of acid secreted and entering the duodenum and the buffering value of the duodenal contents but its action on the secretion of acid was apparently greater than its effect on the secretion of bile, pancreatic juice and juice of the duodenal mucosa. The result of its action was a higher average pH of mixed duodenal and gastric contents when the gastric contents were allowed to enter the duodenum and the mixed gastric and duodenal contents then were aspirated.

Morphine sulfate reduced the volume of the contents of the stomach and of the duodenum promptly and markedly. These drugs usually caused bile to disappear completely within twenty minutes from duodenal contents and to remain absent for three to four hours or more in our fasting subjects who had intact biliary tracts and normally functioning gallbladders. Glyceryl trinitrate and amyl nitrite did not reduce the duration of time during which bile was not found in the duodenal contents. The failure of glyceryl trinitrate and amyl nitrite to induce a flow of bile suggests that their action in reducing the intraductal pressure induced by morphine sulfate in cases in which a T tube is in place in the common bile duct and the gallbladder has been removed may be due to something more than a relaxing effect on the sphincter mechanism with a flow of bile into the duodenum.

Sodium salt of dehydrocholic acid in the dosage given seemed capable of provoking flow of bile great enough slightly to elevate the pH of the fasting gastric and duodenal contents aspirated already mixed, while secretin in dosage given was capable of provoking a secretion of pancreatic juice great enough not only to raise the mean pH to higher levels than ordinarily found or reached after any of the other drugs, but of maintaining the value for pH at or more than neutrality for more than two hours in spite of the entrance of some acid from the stomach into the duodenum. Comparison of the effectiveness of the two drugs in altering the pH of the combined gastric and duodenal contents clearly shows that secretin is far more effective than the sodium salt of dehydrocholic acid in elevating the pH of the duodenal contents during fasting.

The action of atropine sulfate, the sodium salt of dehydrocholic acid and secretin in raising the mean pH of the duodenal contents (gastric and duodenal secretions) during fasting affords a rationale for the use of these drugs in the treatment of peptic ulcer at least during the fasting hours. The clinical value of atropine sulfate in elevating the abnormally low pH of the contents of the duodenum of fasting patients who have duodenal ulcers should be critically examined. The intravenous method and the cost of administration of the sodium salt of dehydrocholic acid and of secretin and possible reactions after the use of "purified" secretin limits their practical application for this purpose at this time. The oral use of bile salts has been suggested in the treatment of peptic ulcer (32, 33) but the relatively small changes in pH of mixed duodenal contents produced by the intravenous administration of sodium salt of dehydrocholic acid indicates that the clinical value of bile salts given either orally or intravenously would be small. The marked and prolonged action of secretin in elevating the pH of the duodenal contents in the observations in which the acid gastric contents were allowed to enter the duodenum and the combined gastric and duodenal contents were aspirated already mixed invites the preparation of a cheap supply of secretin safe for repeated administration and a study of its possible value in the treatment of duodenal ulcer.

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Seasonal Gastroenteritis in Colorado

By

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ALMOST every year Colorado experiences an outbreak of acute gastroenteritis in the early fall. A typical instance is illustrated by the following patient.

Mrs. G. age 50 awoke on Wednesday August 26th with a feeling of nausea, giddiness, vague abdominal cramps followed by the passing of a watery stool containing considerable undigested material. Mrs. G. had been examined carefully two weeks previously because of discomfort in the upper part of the abdomen, gas and belching. The examination included a careful history, physical examination, blood analysis, urine examination, electrocardiograph, basal metabolism, x-ray examination of the stomach, gallbladder and intestines. As a result of the examination, the

complaint had been diagnosed as a gallbladder dyspepsia. The present disturbance did not conform to the previous clinical syndrome; rather it suggested an acute gastroenteritis.

It would have been easy enough to consider the present attack to be an acute gastroenteritis resulting from some dietary indiscretion or from the ingestion of some contaminated foodstuff. However it soon became evident that we were not dealing with a single isolated case, as other cases soon appeared. Within forty-eight hours there were many cases with identical syndromes.

Mrs. G. lived in the east end of town in the Park Hill section of Denver about four miles from the downtown section, whereas Mrs. C. lived on the north side of town about a similar distance from the office; so

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did Mr. L., while Mr. T. lived in a downtown hotel. Mr. S. a salesman just arrived from a small town about thirty-five miles north of Denver to report the same syndrome which he attributed to eating a spaghetti dinner in his pet-peeve hotel. Within forty-eight hours twenty-five people in my practice from almost as many different homes complained of nausea, giddiness, abdominal distress, cramps and diarrhea. Obviously the syndrome could not have resulted from any indiscretion or food poisoning since there was no common food supply to these people. Other physicians reported similar experiences. Soon it became evident that an outbreak of acute gastroenteritis existed which involved the entire metropolitan area of Denver and that it numbered thousands of cases. There was no way to determine the exact number of cases, since these cases were not reported. This outbreak assumed the proportions of a local epidemic. Fortunately practically all the cases recovered within a few days under symptomatic treatment.

Such outbreaks of acute gastroenteritis in the fall of the year are not new in Denver. For some twenty-five years I have been observing them occur with almost clock-like regularity. I have attended many meetings given over to a consideration of these outbreaks and have listened to many acrimonious discussions characterized by heat rather than by light. On one occasion the city water department was accused of negligence, but its champions soon squelched any suggestion of contaminated water being the responsible factor. Then some one suggested that the vegetables were contaminated by being irrigated by untreated sewage water. There arose a great hue and cry. It became so loud that Denver acquired an expensive sewage disposal plant but the epidemics continued just the same. Evidently it was not the fault of the tomatoes and carrots and other vegetables being contaminated by untreated sewage water. Besides similar outbreaks had occurred outside of the Denver metropolitan area where the vegetables had had the best of pure mountain water quite free from any taint of pollution.

Now no one regrets the erection of a sewage disposal plant in Denver which we consider a sign of progress in safeguarding the community health, but the fact remains that the erection of a sewage disposal plant did not solve the problem of seasonal gastroenteritis.

Some years ago when I first became intrigued with the problem, I requested the bacteriology department of the University of Colorado to conduct some studies in one of these outbreaks. About twenty-five patients who had developed the symptoms had cultures made on their blood and stools. The twenty-five blood cultures remained sterile and twenty-four of the stool examinations gave nothing of importance. The twenty-fifth patient showed a paratyphoid infection in the stool. However this patient upon investigation was found to have been visiting a neighborhood farm where the outhouse and water supply were uncomfortably close together. So nothing came of this bacteriologic study.

Pondering over these seasonal outbreaks and searching for a common denominator, the only factor that I can think of that is common to all of them is that they occur in the fall of the year usually after a dry spell when the air has been dusty for some time. It is possible that they are related to the dust and that the dust is a carrier of something else which is either inhaled or ingested and that something could be a virus.

Other observers have pondered over this same problem. Dack (1) reports an epidemic of acute gastroenteritis which involved 48 persons residing in dormitories at the University of Chicago. The outbreak did not appear to have been spread through the medium of food or water. Laboratory studies did not reveal the causative factor responsible for the illness. The epidemiological features suggested contact or droplet infection, although attempts to reproduce the disease in monkeys with nasopharyngeal washings and blood from the patients were unsuccessful.

Smith and Davies (2) report their experience with an epidemic of gastroenteritis which occurred in the British troops in a large training area. The epidemic occurred in the middle of December. It was not limited exclusively to the military population but also included some of the adjacent civil population. They made exhaustive bacteriologic studies on the food and excluded the common causes of contamination as typhoid, paratyphoid, dysentery, food poisoning due to staphylococci and streptococcus. They suggest that it is possible that the outbreak was due to a virus infection similar to the so-called gastric influenza of the gastrointestinal type of distemper in dogs or swine fever in pigs. Kantor (3) agrees with this suggestion and states that the epidemiologic features suggest contact or droplet infection and a possible virus infection.

DISCUSSION

In the routine practice of medicine, the physician encounters many syndromes which present diagnostic problems. One group which is quite troublesome is the class which possesses some characteristics of infections yet which conform to no established type of infectious disease.

Infectious diseases whose causative agents are visible under the ordinary microscope as those due to protozoa, bacteria, fungi and the spirochetes have been fairly well identified; but the virus diseases present tremendous difficulties in identification.

It is possible that some of our diagnostic problems fall into the group of virus infections awaiting future studies to establish their identities.

Viruses are infectious agents whose exact nature is unknown although some of their characteristics have been established. They are small and propagate solely with the cell; they contain nucleoprotein, generally they are slender rods or spherules in form, although different types vary from each other in size and shape. They are considerably smaller than ordinary bacteria and are measured in terms of millimicra rather than in micra. Because viruses have a size considerably smaller than ordinary bacteria they are filterable which

implies a size less than 0.2 micra. Generally they are not visible under the ordinary microscope, however under the electron microscope some of them become visible.

The outstanding characteristic which differentiates them from bacteria is their ability to propagate only in the presence of living cells; in other words they are obligate parasites incapable of independent existence outside of their hosts; yet some of the viruses of plant disease such as the virus of tobacco mosaic disease have been crystallized which raises the question whether they are animate or inanimate agents. However it must be born in mind that in a broad biologic sense there is no sharp line of cleavage between animate and inanimate objects. This line of cleavage ceased to exist in 1828 when Wohler synthesized urea from inorganic constituents and bridged the gap between organic and inorganic substances. It may be that viruses represent one of these "missing links" between living and inanimate objects.

Some viruses have been identified clinically. These are the causes of: (1) disease of childhood as cow pox, small pox, chicken pox, measles, mumps; (2) diseases of the central nervous system as encephalitis, lymphocytic choriomeningitis, poliomyelitis, rabies; (3) systemic diseases as influenza, foot and mouth disease, yellow fever, dengue, psittacosis; (4) surface diseases as herpes simplex, herpes zoster, molluscum contagiosum, warts, lymphogranuloma inguinale; (5) tumors as Shope's papilloma and Rous' sarcoma.

Goodpasture (4) has divided viruses into three groups. The first group affect the skin only, they cause warts, molluscum contagiosum, etc, they are epitheliotropic and do not enter the blood. The second group cause systemic infections as small pox, measles. This group of virus enters the blood presumably through the upper respiratory tract then localize in the skin. The third group affect the central nervous system, they are obligate neurotropic, they cause poliomyelitis, rabies, etc; these also enter the blood through the upper respiratory tract and then are localized in the nervous system. However some viruses may affect more than one type of cell; they are spoken of as polytropic.

Often the existence of viruses is known only through the results of their activity in susceptible hosts. However some viruses can be grown by inoculating suspected material into susceptible animals or chick embryos.

One of the demonstrable evidences of the presence of virus infection is the presence of intracellular inclusion bodies within the cells which are evident as well defined globular masses within the cytoplasm; they appear to be homogeneous with ordinary stains; although some of them may contain net like structures.

Some viruses produce an inflammatory reaction characterized by lymphocytic infiltration rather than by polymorphonuclear infiltration; however Rivers (5) believes that the inflammatory reaction is secondary to primary changes of proliferation and degeneration of the infected cells. In his experimental studies with

the virus of small pox he found that proliferative and degenerative changes appear within 3 to 6 hours after inoculating the cornea of a rabbit, whereas the inflammatory changes do not appear until about 48 hours after inoculation.

Viruses sometimes produce tumors as Shope's papillomas and Rous' sarcoma which are considered to be examples of virus hyperplasia. At times benign virus tumors may become malignant. This change from the benign to the malignant state is due to a change in the characteristics of the virus (Rivers). The fact that viruses have been shown to cause these types of tumors does not warrant the generalization that they are the cause of all tumors.

Most viruses are spread by contact or droplet infection, that is, by transmission from one host to another; a few however are spread by insects. The spread of virus diseases differs in no way from the spread of other infectious diseases.

The basic principles of immune phenomena are operative in virus diseases as elsewhere. Viruses are capable of producing protective humoral antibodies in the sera of invaded hosts. In fact the first application of protective vaccination anywhere occurred in a virus disease, when Jenner in 1796 began his experiments with the human inoculation of the virus of cow pox as a protection against small pox. The type of immunity that exists or which may be developed in an individual is divided into the three usual grades; namely natural, active and passive. Acquired immunity in virus diseases is very elastic and relative. It may be life long or it may be fleeting.

The state of nutrition of an individual or his general health or the vitamin level has little influence on his susceptibility to virus infections.

Viruses are capable of producing a multiplicity of reactions within the body. These include immune phenomena, hyperplasia, degeneration, lymphocytic infiltration, secondary inflammatory reaction, fever, tumor formation, etc. No direct explanation can be given to this multiplicity of phenomena because the nature of viruses themselves is unknown. Quite likely there are different kinds of viruses with each type possessing specific characteristics. This very multiplicity of characteristics of viruses opens up a possible explanation for some of the troublesome problems which are encountered in the practice of medicine.

In the treatment of virus disorders, prophylaxis has proved of tremendous value in some diseases, as in the vaccination for small pox, rabies and yellow fever, but not in others. Vaccines for encephalitis and influenza are being studied, and there is every reason to believe that eventually other protective vaccines will be developed.

Quarantine is helpful in a few instances as in yellow fever where the control of the insect vectors has proved of value but generally speaking quarantine and isolation are of little value because the infection literally travels with the wind through the medium of droplet infection.

The use of convalescent sera has proved of some merit in those cases where the serum can incite the production of antibodies in the host and establish an immunity before the onset of the disease itself as in measles.

The sulfa drugs thus far have proved a disappointment, and many physicians believe their use is dangerous because it creates a false sense of security. Specific chemotherapy nevertheless offers great possibilities for future studies. Chemical blockade by the application of simple chemical substances to the nasal mucous membranes as picric acid or zinc sulphate have proved disappointing. There is no evidence that the use of chemical blockade prevents infection.

Once the virus has entered the cells of the body, little can be done to influence the disease, and the treatment becomes symptomatic and consists of rest, good food, good nursing, general hygiene, physiotherapy, anti-spasmodics, sedatives and supportive measures.

Much remains to be discovered concerning the nature of viruses. It seems fair to state that only a beginning has been made in the understanding of this type of infection and that future studies will help to solve many of the diagnostic and therapeutic problems of today.

SUMMARY

1. Almost every year Colorado experiences an outbreak of acute gastroenteritis in the early fall.
2. Bacteriologic studies of the blood and stool of the patients have given no information as to the nature of the infection.
3. There is no apparent reason for suspecting food infection, water infection or sewage contamination.
4. The epidemiologic features of the outbreaks suggests a contact or droplet infection.
5. The possibility of a virus infection is to be considered.
6. Until the nature of viruses is better understood, the control of these seasonal outbreaks of acute gastroenteritis will probably be unsatisfactory and the treatment will remain symptomatic.

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Effect of Lemon Juice on Pepsin Activity between pH 2.4 and 4, the Range of Achlorhydria*

By

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IT has been previously reported (1) that over a pH range of 1.1 to 2.4 orange and lemon juices accelerate the action of pepsin on freshly cooked egg albumen.

The clinical work of Sansum and Gray (2) showed definite improvement of achlorhydria patients when lemon juice was added to the diet. The work now reported was undertaken to obtain *in vitro* data to show the effect of lemon juice on peptic digestion within the pH range of achlorhydria (2.4 to 4).

Using the same technique as in the previous experiments, with freshly cooked egg albumen as substrate, experiments have been conducted to cover the pH range of 2.4 to 4. In these experiments lemon juice only has been tested for its ability to accelerate peptic activity. The lemon juice used in these experiments had the following composition:

Acid (as anhydrous citric) 4.82%
Total Soluble Solids (by refractometer) .. 7.12%
pH 2.4

In a single series it is difficult to prepare and ob-

serve more than a limited number of freshly cooked egg albumen strips. Therefore, in extending the environmental pH the observations in the previously reported pH range were not repeated. Figure 1 includes

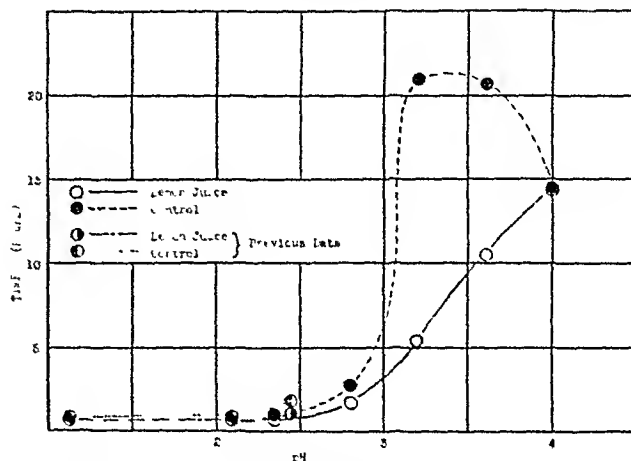


FIGURE 1.
Effect of Lemon Juice on Peptic Activity,—in Aqueous Solution.
the old data from pH 1.1 to 2.4 and the present results of Series 1 up to pH 4.

*From Research Department, California Fruit Growers Exchange, 616 East Grove Street, Ontario, California.

In Series 1 (see Table 1) aqueous solutions of pepsin containing lemon juice, the pH values of which were adjusted by the addition of 0.1 N HCl or 1 N NaOH as necessary, were compared to controls without lemon juice but adjusted to the same pH by the addition of 0.1 N HCl.

TABLE 1

Series 1. Effect of Lemon Juice in Aqueous Solution on Peptic Activity, Using Freshly Cooked Egg Albumen Strips as Substrate

Strip No.	pH Adjusting Solution			H ₂ O	Total Volume	Pepsin	pH	Breaking Time	Average Breaking Time	
	Lemon Juice	0.1 N HCl	1 N NaOH						Minutes	Hours
A	10 ml	4.0 ml	—	16.0 ml	30.0 ml	100 mg	2.35	41		
B	Duplicate of A							42		0.7
C	none	3.25 ml	—	26.75 ml	30.0 ml	100 mg	2.35	61		
D	Duplicate of C							*		1.0
E	10 ml	—	0.3 ml	19.7 ml	30.0 ml	100 mg	2.80	115		
F	Duplicate of E							87		1.7
G	none	2.0 ml	—	28.0 ml	30.0 ml	100 mg	2.80	**		
H	Duplicate of G							161		2.7
A-1	10 ml	—	1.1 ml	18.9 ml	30.0 ml	100 mg	3.20	309		
B-1	Duplicate of A-1							310		5.2
C-1	none	0.9 ml	—	29.1 ml	30.0 ml	100 mg	3.20	1346		
D-1	Duplicate of C-1							1163		20.9
E-1	10 ml	—	2.1 ml	17.9 ml	30.0 ml	100 mg	3.60	610		
F-1	Duplicate of E-1							646		10.5
G-1	none	0.6 ml	—	29.4 ml	30.0 ml	100 mg	3.60	1344		
H-1	Duplicate of G-1							1130		20.6
E-2	10 ml	—	3.2 ml	16.8 ml	30.0 ml	100 mg	4.00	838		
F-2	Duplicate of E-2							878		14.3
G-2	none	0.1 ml	—	29.9 ml	30.0 ml	100 mg	4.00	869		
H-2	Duplicate of G-2							862		14.4

* Strip accidentally broken in setting up experiment.

** Strip defective, broke with but little digestion

Lemon juice effects acceleration of peptic activity in this higher pH range: the most pronounced influence occurring at somewhat above pH 3 and almost dis-

TABLE 2

Series 2. Effect of Lemon Juice in Normal Saline Solution on Peptic Activity, Using Freshly Cooked Egg Albumen Strips as Substrate

Strip No.	pH Adjusting Solution			Normal Saline Solution	Total Volume	Pepsin	pH	Breaking Time	Average Breaking Time	
	Lemon Juice	0.1 N HCl	1 N NaOH						Minutes	Hours
I	10 ml	2.5 ml	—	17.5 ml	30.0 ml	100 mg	2.38	107		
J	Duplicate of I							126		1.9
K	none	3.15 ml	—	26.85 ml	30.0 ml	100 mg	2.58	193		
L	Duplicate of K							223		3.5
M	10 ml	—	0.95 ml	19.05 ml	30.0 ml	100 mg	3.00	373		
N	Duplicate of M							353		6.0
O	none	1.25 ml	—	28.75 ml	30.0 ml	100 mg	3.00	724		
P	Duplicate of O							730		12.1
E	10 ml	—	1.6 ml	18.4 ml	30.0 ml	100 mg	3.40	628		
F	Duplicate of E							595		10.2
G	none	0.95 ml	—	29.05 ml	30.0 ml	100 mg	3.40	1035		
H	Duplicate of G							1064		17.5
A	10 ml	—	2.95 ml	17.05 ml	30.0 ml	100 mg	4.00	1021		
B	Duplicate of A							952		16.4
C	none	0.3 ml	—	29.7 ml	30.0 ml	100 mg	4.00	846		
D	Duplicate of C							1196		19.9

appearing as pH 4 is attained. It should be stated that at the time of breaking at pH 4 the albumen strips

had more the appearance of an embrittlement than of a true peptic digestion.

The peculiar shape of the control curve (without lemon juice) between pH 3 and 4 forced us to recognize certain differences in the systems.

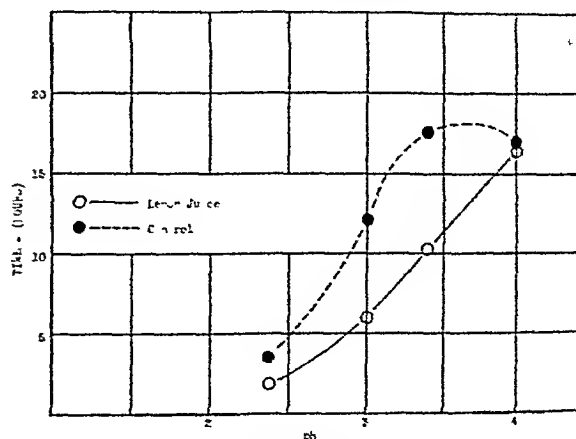


FIGURE 2.

Effect of Lemon Juice on Peptic Activity,—in Normal Saline Solution

Obviously the osmotic pressures were different, being higher in all cases where lemon juice was included and especially at the higher pH values where alkali was also added. At these same high pH values the control samples contained the minimum amount of HCl or other solute.

Consequently the work of Series 1 was repeated in Series 2 (see Table 2) covering the same pH range but with all solutions made in normal saline (0.9% NaCl). Figure 2 shows the results. At pH 4 cm-

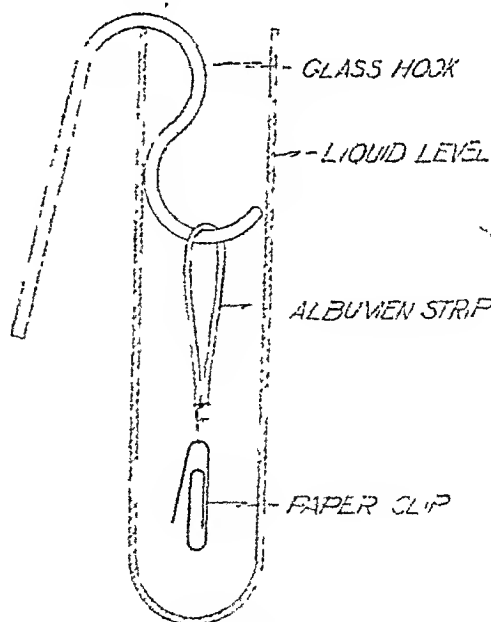


FIGURE 3.

Equipment and Setup for Testing Peptic Activity.

brittleness of the albumen was again observed possibly due to approaching the isoelectric point of the egg albumen. The accelerating effect of lemon juice is

quite in evidence in the intermediate pH range. The curves representing isotonic solutions (Figure 2) are more regular and certainly more significant than those of Figure 1 if the results are to be considered as to their possible application *in vivo*.

The author wishes to give credit to Mr. W. E. Baier for suggesting the use of normal saline solution in the Series 2 experiments. He also wishes to thank both Mr. Baier and Mr. J. W. Stevens for criticism of this paper.

SUMMARY AND CONCLUSIONS

1. Lemon juice accelerates the activity of pepsin between pH 2.4 and 4 whether measured in aqueous solution or in normal saline solution.

2. Peptic acceleration due to lemon juice is greater in isotonic solution at pH 2.4 to 3 than in aqueous solution. Between pH 3 to 4 the reverse is true: lemon juice accelerates in aqueous solution more than in isotonic.

3. In the intermediate pH range of 2.4 to 3 a longer digestion period is required in isotonic than in aqueous solution.

4. In the presence of lemon juice the curves representing aqueous and isotonic solutions run nearly parallel throughout the pH range of 2.4 to 4.

5. Embrittlement was observed at pH 4, at which pH lemon juice is without significant effect on the digestion time. Possibly these phenomena at pH 4 are due to approaching the isoelectric point (pH 4.86) of egg albumen.

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Familial Peptic Ulcer Hemorrhage

By

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WHEN one inquires into the cause of gastric or duodenal ulcer, the statement generally offered in the current text books of medicine is "the cause (1) of peptic ulcer is unknown." A variety of theories and concepts are then set forth in enumeration of the many factors entering into the etiology. Among those that are mentioned are bacterial infections which allegedly bring resultant emboli or thrombi formation and consequent necrosis. Tobacco at times is included as a causative agent. Its effects on the ganglion cells or upon the higher nerve centers has been regarded as a potent factor in producing gastric or duodenal ulceration. Trauma through local injury, the ingestion of spices, foods or drink which are excessively hot, general body burns, have all had their claimants in an attempt to explain its cause. Among the more recent contributions have been those in the realm of the patient's nervous system. Cushing (2) was one of the early workers to focus the origin of ulcer in this locality. He underscored the occurrence of frequent acute ulcers after operations on the cranium as well as their association with tumors appearing simultaneously in the mid-brain and diencephalon. It was his belief that the parasympathetic center in the hypothalamus occasioned stimuli which were conveyed along the vagus nerve thus bringing about mucosal changes of the organism.

Through experimental means, Beattie (3) succeeded in producing erosions of the lesser curvature of the stomach by stimulation of the hypothalamus in the region of the tuber cinereum. Keller (4) and his associates added their interesting observations of ulcer-

ations of the stomach and duodenum following lesions of the hypothalamus. The liberation of histamine through vagal stimulation and subsequent increased acid content of the gastric juice was offered by Babkin (5) as inducing an impaired local blood supply and resulting mucosal ulceration. The glandular aspect of ulcer etiology found expression in the observations of Dodds (6) and his co-workers who noted that pitressin or pituitrin could bring about superficial necrosis of the mucosa as a consequence of vascular spasm. A. F. Hurst (7) wrote "that despite the frequency of the familial history of gastric and duodenal ulcer, mention of this finding is not contained in large books on diseases of the stomach or duodenum." It is stated by Meakins (8) "it is not unusual to find a familial tendency to ulcer formation." Histories often yield information suggesting similar conditions either in the direct family line or amongst more distant relatives. In this respect ulcer seems to be no more prominent than in the oft recurring instances where heredity plays a part in other affections of the gastro-intestinal tract such as cholelithiasis, carcinoma etc. Yet there are certain features of interest in the familial aspects of ulcer in consideration of which Hurst adds "that he never saw a member of a family in whom the presence of a gastric ulcer was proved and in whom the presence of a duodenal ulcer was certainly established." It is thereby suggested that certain types of stomachs predispose to the development of gastric and duodenal ulcer respectively and these factors are congenital."

One could scarcely admit at this time that were such a predisposition to ulcer acceptable as an etiological

factor, that such a tendency of itself could serve to explain not only the individual peculiarities of the ulcer itself in addition to other items such as its anatomical location, tendency to hemorrhage and perforation, degeneration, etc. Many supporters today cling to the supposition that a gastric or duodenal diathesis exists which leads to the development of ulcer under certain conditions which would have no such effect in normal individuals. While discussions relative to the cause of ulcer have been numerous, nowhere in the author's experience nor in the search of literature could there be found a record which chronicles the presence of ulcer in several members of the same family, whose basic characteristic is the occurrence of massive hemorrhage.

It might be well to indicate at this point that while bleeding from an erosion or ulcer might not be considered an unusual phenomenon in the life of an ordinary ulcer patient, such loss of blood being usually of a microscopic variety, when however it manifests itself as a hematemesis or melena, its seriousness soon makes itself felt with the patient.

The cases to be presented offer more than a passing interest, for six closely related members of the same family were affected one time or other by a marked blood loss as a complication to a preexisting peptic ulcer. The one first to be involved is Mrs. S. B., the mother of eleven children, of whom there were nine sons and two daughters. Of these, four sons and one daughter had a peptic ulcer with massive hemorrhage. A daughter of the eldest son likewise was similarly afflicted. The remainder of the children, aside from another daughter, who had had a gastro-intestinal affection (not ulcerous), had no digestive disturbances as far as could be ascertained. At the age of 86, she was admitted to the Presbyterian Hospital in New York in June 1936. (Case No. 489188). A history of long standing upper abdominal pain had existed with a recent melena. X-ray studies revealed the presence of a gastric ulcer. She died from hemorrhage which could not be controlled despite repeated transfusions.

G. V. B., a son, 47 years old, a physician, had a large hemorrhage without previous prodromal symptoms, from which he recovered after medical treatment while a patient likewise at the Presbyterian Hospital. The cause was a duodenal ulcer. He had but a few symptoms later only to experience a similar episode of gross bleeding in the form of tarry stools. Occasional heartburn without any pain has been experienced from time to time. He has been maintained on a relatively restricted diet.

Another son, H. A. B., 54 years of age was admitted on May 21, 1938, to the Orange Memorial Hospital, in Orange, N. J., with a diagnosis of duodenal ulcer and secondary anemia. His admission note stated—"ten days ago the patient had a series of very serious hemorrhages from his stomach. Totally, a large quantity of blood was lost. He became very weak and could work no longer. All of his stools for one week following were quite black with old blood." This patient had noted several attacks of stomach trouble associated with pain and a complete ulcer syn-

drome from which previously he had always recovered. While at the hospital he was transfused three times with 500 cc. of whole blood on each occasion. The lowest hemoglobin reading reached 55% and the red blood cell count was 2,850,000. Upon x-ray examination, the existence of a definite duodenal ulcer was established.

F. B., a third son, aged 53, has complained of ulcer pains for many years. In 1924 hematemesis and melena were first experienced for which he was admitted and treated at Bellevue Hospital. Subsequent to this, another episode of a similar nature occurred nine months later for which he was readmitted to the same institution. At this time a gastro-enterostomy was performed, only to experience a gross hemorrhage three months later when he entered the Presbyterian Hospital. Three future recurrences of blood loss took place at varying intervals culminating in the performance of a subtotal gastrectomy at the St. Luke's Hospital three years ago. There have been two massive hemorrhages since. Typical ulcer pains have prevailed in the interim. The x-ray report as well as operative diagnosis confirmed the existence of a duodenal ulcer as the basis for his trouble.

W. B., age 63, a fourth son, had been suffering from the effects of a duodenal ulcer for a period of over twenty-five years. On March 23, 1937, he was admitted as a patient to the Mary Immaculate Hospital in New York with a diagnosis of bleeding duodenal ulcer. At the time of admission his hemoglobin value was 60% and the red cell count reached 3,090,000 for which he was transfused. On the following day, 500 cc. of blood was similarly administered. Notwithstanding all efforts in his behalf, the patient became steadily worse and expired on March 29, 1937. At autopsy, the findings revealed the presence of a hemorrhage into the gastro-intestinal tract arising from a duodenal ulcer. This last son had a daughter.

Mrs. M. B., age 45 years. Seventeen years ago she was operated upon at the St. Johns Hospital in Long Island City at which occasion her appendix was removed. The operative note likewise revealed a healed ulcer. Eight years ago, a subtotal gastrectomy was performed at the St. Luke's Hospital. This latter procedure appeared to give the desired relief for a while only to be followed by four massive hemorrhages which prior to gastrectomy were non-existent. At the present time she has a jejunal ulcer which is productive of considerable discomfort and for which she is obtaining the required treatment. Her first admission for hemorrhage took place on Oct. 3, 1937, at the Mary Immaculate Hospital where a bleeding ulcer was diagnosed. Two transfusions were given and the patient was eventually discharged with a hemoglobin of 66% and a red cell count of 3,300,000. In 1940 she was admitted to the Jamaica Hospital for a similar hemorrhage, and nine months ago, she again noted tarry stools and an accompanying anemia. Pain and bloating have been common symptoms from time to time.

A daughter of S. B., who was the first patient considered in this series, Miss M. B., age 63, likewise

sought admission to the Presbyterian Hospital on August 3, 1943. (Case No. 716531). She had had ulcer symptoms for many years and had a gastric resection performed because of her past symptoms. Notwithstanding this, a massive hemorrhage took place reducing her blood content to a hemoglobin value of 47% and 2,200,000 red blood cells. With the aid of transfusions she responded to treatment and was discharged from the hospital on September 9, 1943. X-ray studies at the hospital revealed the presence of duodenal ulcer.

COMMENT

That the human constitution as such determines if not influences in some measure the life cycle of a peptic ulcer is generally recognized. By no means however does it offer a complete answer to the establishment of the actual etiology. It might well be, that with a basic pattern that is affected, initiating influences may come into play where ordinarily they would have no influence. Many instances unmistakably exist where no familial or constitutional weakness is ascertainable, and yet the ulcer syndrome finds place for its existence. While the involvement of several members of a family in itself is of interest, the suggestions and implications which six close blood relatives, all of whom experienced the same complications of massive hemorrhage in each instance establishes a meaning of possible significance. Does the stigma of a family trait alter the clinical course and suggest certain considerations as to therapy? Is it possible that an ingrained factor of a familial existence of peptic ulcer predicates a basic disorder of such a nature as to guard one in applying the same principles of treatment ordinarily employed in patients not so disposed? It might be pointed out that

in the case of Miss M. B., a gastric resection was performed for long standing ulcer complaints. At no time prior to the operation had she been afflicted by bleeding, and yet the operation far from curing her, was followed by a gross hemorrhage. Similarly, F. B.'s operation was entirely unsuccessful, for it was followed by several incidents of marked blood loss from the stomach as well as rectally. Mrs. M. B. seems to have fared no better. She too was operated upon with results comparable to the other two. In a study of one (9) hundred and eight cases of massive ulcer bleeding, a 42% incidence of recurrence was established. It may be advisable that further analysis be given to the influence of the constitutional factor as a consideration of basic importance in this important problem.

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Lesions of the Small Intestine^{*}

By

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QUITE a number of papers relating to Roentgen ray studies of these lesions have appeared in the recent literature, but the authors have either not understood or mentioned the classical work of Dr. R. Walter Mills on this subject. His first paper (1) on *the relation of bodily habitus to visceral form, position, tonus and motility* was published in 1917. He made x-ray examinations of one thousand persons and formulated the theory that mankind was divided into four different physical types, which he classified as *hypersthenic, sthenic, hyposthenic and asthenic*.

His article pertaining to *the incidence of bodily habitus and the time of complete gastric motility in different types of habitus* appeared in 1922 (2). In this study he discussed the incidence of disease occurring in

different types of bodily habitus and emphasized the fact that it was not only demonstrated in the gastrointestinal tract, but was expressed in every organ and tissue of the body.

His last great epoch making work was published in 1922, entitled "*X-Ray Evidence of Abdominal Small Intestinal States Embodying An Hypothesis of The Transmission of Gastro-Intestinal Tension*." (3) In this paper he stated that the small intestine bears the same relation to habitus as does the stomach and colon as to form, position, tonus and motility. In sthenic types the arrangement of the whole is higher, the coils are more discrete, of different arrangement, a demonstrably greater degree of tonus and a more rapid motility than in asthenic and hyposthenic subjects. Under normal conditions the appearance of the small intestine on the plate is characteristic, judged on the

* The x-ray films are omitted in this article because of lack of space. The reader is referred to the original paper.
Submitted Nov. 26, 1943.

basis of physical type. In brief, he formulated the basic principles on which Roentgen diagnosis of the small intestine must rest. He showed 62 films depicting the normal pattern in various types of bodily habitus with deviations from the normal in pathologic conditions. It is interesting to note that these films are not inferior to the modern ones with all our improvements in Roentgenology.

Mills' technic is as follows:

First: The patient must be examined in the upright posture.

Second: Begin to look for abnormalities in the small intestinal pattern from the two-and-one-half to the six-hour period. They are very often observed just about the time the last part of the barium meal leaves the stomach.

Third: Secure a film of the suspicious area at once and continue to watch for other overfilled loops, and plate at once. The shadows are apt to be evanescent. It is a mistake to expect them to be persistent. Remember that you are searching for evidence of partial and not complete obstruction.

Following this method I have demonstrated many lesions in the small intestine. (4, 5) The differential diagnosis between diverticulum and carcinoma deserves particular emphasis. In diverticulum the shadow persists a longer time, after 24 hours or more and the occult blood reaction in the feces is negative, while in carcinoma the shadow is never persistent and the occult blood reaction is present on a flesh-free smooth diet list, moreover, the carcinoma is frequently surmounted by a gas bubble which I have never observed in a diverticulum. In sarcoma the shadow is persistent, usually irregular in outline and an occult blood reaction occurs in every specimen of feces. Multiple diverticula of the jejunum and duodenum are rare—but two cases observed in our series.

Tuberculous lesions and metastatic carcinoma are difficult to differentiate by the x-ray films: as a rule the finding of tubercle bacilli in the feces, or localization of the primary carcinomatous growth establishes the diagnosis.

J. T. Case (6) corroborated Mills' work on x-ray of the small intestine and emphasized that while 24-hour stasis in the ileum must be regarded as a pathologic condition, the 9-hour film may show an empty ileum. Iegurgitation from the cecum may reveal barium in the ileum on the 24-hour observation.

The study of shadows produced by adhesions is instructive in diagnosis and treatment. (7) Atypical patterns may be found in nearly all patients who have been subjected to abdominal section. They are more irregular in form than the smooth normal pattern, but as a rule produce no symptoms. Strong bands of adhesions may cause periodical attacks of partial obstruction. They show in the x-ray film as dilated loops, and a gas bubble above the barium level is a frequent finding. They are very amenable to correction by surgery.

Extra-alimentary growths may produce distortion and displacement of the small intestinal loops by pres-

sure, or the gut may become adherent to the tumor mass.

Chronic catarrhal enteritis is often a complication in achylia gastrica. A low grade inflammatory process can be demonstrated by a close study of the feces: the smear will show microscopically undigested muscle fibres, excess of starch granules and small clumps of mucous in which are enclosed a number of leucocytes. In a recent paper (8) I have demonstrated that the intestinal protozoa, particularly the trichomonas hominis and entamoeba coli may produce a catarrhal enteritis, which when the host is invaded by an infectious agent, may become highly pathogenic and cause severe Acute Regional Ileitis.

The chronic form of Regional Ileitis has been well described as a clinical entity by B. B. Crohn. (9) P. W. Brown. (10) J. A. Bargen (11) and others. It may involve any segment of the small intestine, but the vast majority of cases are limited to the terminal ileum; surgical intervention is always indicated.

(12) I must again emphasize the importance of the occult blood test in the feces, especially the guaiac test, inasmuch as the benzidine, phenolphthalein and other tests are too sensitive to be relied upon. In 6 cases of our series of carcinoma of the small intestine it was the only positive one, all the others including x-ray of the entire gastro intestinal tract were negative in character.

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The Interdigestive Discharge of Duodenal Content in Man

By

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THE term "discharge" represents the output and not the secretory activity. The discharge is the resultant of 1. secretory activity, 2. retaining and opening function of the sphincters of Oddi and Boyden, 3. filling, concentrating and emptying function of the gall bladder.

The studies do not deal with the "digestive" discharge and therefore not with the emptying function of the gall bladder. They are confined to the so-called "interdigestive" discharge, which occurs spontaneously in the fasting state, in the interval between the digestive stimuli.

The "duodenal content" discharged in this interdigestive phase does not possess the dark brown color which is due to emptying of the gall bladder with subsequent admixture of gall bladder bile, but has a golden color and consists of four, as a rule simultaneously discharged secretions; 1. liver bile, 2. pancreatic secretion, 3. secretions of the glands of the bile ducts, 4. secretion of duodenal mucosa. This entire fluid represents a functional digestive unit. Various terms are used for it, such as "duodenal content," "biliary-pancreatic secretion" or just "liver bile" as an abbreviation and justified only as a *pars pro toto* denomination.

The existence of discharge in the interdigestive phase and without emptying of the gall bladder is frequently overlooked in physiologic considerations of the subject but it is suggested on a broad basis in man by duodenal drainage. Details were studied by Boldyreff (1) and Anithkov (2) about forty and thirty years ago. They described the periodicity of this drainage in man as it was done previously in animals. Since then few systematic studies have been performed in man and our present knowledge of the subject is scarcely adequate. However, the interdigestive discharge represents the physiological pattern of all function tests which utilize the duodenal content. Further studies, therefore, are not only of theoretical but of practical value.

METHOD OF QUANTITATIVE DRAINAGE

The preliminary step towards further insight into the matter was to develop a method which drains the "duodenal content" quantitatively, that is, without loss into jejunum or stomach and without dilution due to inflow of gastric juice. Studies of the physical and physiological factors which influence the drainage output revealed that such a drainage can be accomplished when a continuous and sufficient suction, adequate

drainage tubes, and removal of the gastric fluid are employed (3, 4). The crucial experiment for the loss downwards was done by means of one tube in the duodenum and another drainage tube in the jejunum. The output from both tubes was led into a separate series of test tubes, changing the test tube every five minutes. There was a regular flow of fluid from the tube in the duodenum, however no fluid or only negligible amounts were obtained from the jejunum over long periods of observation, thus proving that loss of fluid downwards can be avoided. In all subsequent experiments the second drainage tube was not in the jejunum but in the stomach so that gastric juice could be drained off. By these means inflow of gastric juice into the duodenum was prevented entirely or at least for long periods of time and incidental reflux of duodenal content into the stomach could be taken into consideration.

Investigation of three questions was made possible by the use of the quantitative drainage: 1. periodicity, 2. rhythm, 3. amount of the interdigestive discharge. This was done in thirty-five drainages on healthy individuals and in individuals with biliary diseases. It was necessary to extend the drainages in the fasting state up to three or even six hours.

PERIODICITY

To study the periodicity, the drainage output was "fractionated" every five minutes in a separate tube (see fig. 1). An empty tube indicates absence of discharge in the respective five minute interval. Series of empty test tubes form "*periods of stoppage*" of discharge. The first lasted for three test tubes i. e. fifteen minutes, the second for eight test tubes i. e. forty minutes. The stoppages between the periods of discharge can be called "*interperiodic*" stoppages. Conversely a filled test tube indicates presence of discharge. The filled test tubes form more or less connected "*periods of discharge*." In figure 1 they lasted for 50, 35 and 40 minutes. The period of discharge itself does not present a continuous flow but a *discontinuous series of pushes* with some "*intra-periodic*" stoppages in between. Intraproperiodic stoppages which last more than five minutes are demonstrated in figure 1.

Shorter stoppages and further details of discharge were analyzed by means of a graphic method. The drainage output was led into a large U tube water manometer with a writer and the discharge into the duodenum was registered on a kymograph for five minutes. Every five minutes, the inflow was rapidly removed from the manometer and the tracing was commenced again. In these tracings stoppage was indicated by a horizontal line, slow dribbling by a slight-

This paper was presented at the special meeting of the Rudolf Virchow Society, New York in honor of the seventieth anniversary of Dr. Otto Loewi, June 4, 1943. The investigations were carried out in the clinic for the study of diseases of the liver and biliary tract at the New York Post-Graduate Medical School and Hospital, Columbia University, in great part with the collaboration of Dr. Elliot Oppenheim and aided by grants from the Oliver Rea Fund, New York Post-Graduate Hospital, and from the Sandoz Chemical Works, New York City.

ly increasing line, quick dribbling by a steep line and a gush by a nearly vertical line. The amount could be estimated from standard marks of discharge. For instance, an entire period of discharge embracing eight five minute periods and limited on both sides by periods

inhibits the discharge; others believe the tube stimulates discharge. It is not likely that, as for instance in figure 1, in the same patient the tube stimulates and inhibits alternately. In our experience the introduction of the duodenal tube exerts only occasional and rather

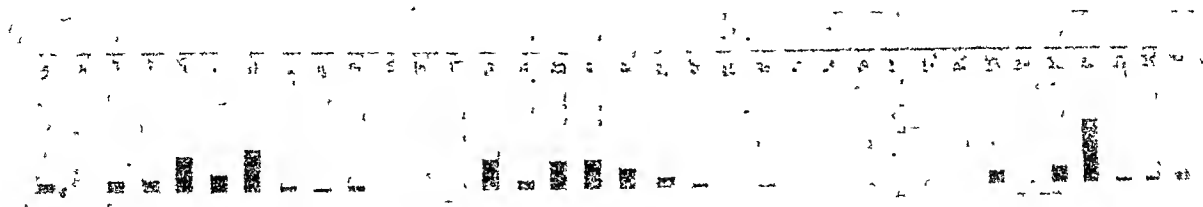


FIGURE 1.

Periodicity of the Interdigestive Discharge of Duodenal Content.

of stoppage was recorded. The period opened as usual, with a very slow dribbling for about two minutes and not with a flood of retained and dammed up fluid,—then a small gush followed—a short stoppage—quick dribbling for about two minutes—slow dribbling for five minutes—then quick dribbling for three minutes and so forth, until at the peak of the discharge, when 10 cc. in five minutes were delivered, rhythmic gushes with complete interruptions and steplike tracings set in. Minute dribbling for about ten minutes occurred at the conclusion of the period.

The drainage output under the described conditions resembled the bile discharge which can be seen at the experimentally exposed papilla of Vater in animals. This demonstrated how closely this drainage approaches the actual discharge.

The length of the interperiodic stoppages underlies larger individual variation than Boldyreff assumed. Three main types of interdigestive discharge may be classified, thus far: 1. the medium stop type, 2. the long stop type, 3. the short stop type including the non stop type.

The *medium stop type* is illustrated by figure 1. In the *long stop type* the period of stoppage may last for two hours and more. The stoppage can be very intensive and persistent. Mechanical and thermal stimuli frequently do not overcome it, but chemical stimuli usually break the stoppage. The long stop type can be characteristic for a certain individual. It was found for instance, in the same person six times without exception within 1½ years; other individuals present a certain variation of the type at different drainages. It has been found exclusively in patients possessing a functioning gall bladder. The *short stop type* presents very short interperiodic stoppages and the *non stop type* presents practically none. The short stop type of discharge has been found regularly in patients with cholecystectomy, a fact which correlates with the experimental findings in cholecystectomized animals, in which a tendency to continuous dribbling is described.

The question that now presents itself is how do periods of stoppage and subsequent periodicity come about? Some investigators express the opinion that it is the introduction of the tube into the duodenum which

transient stimulation when vomiting is avoided. Spontaneous stoppages and discharges rule the picture. The alternation of stoppage and discharge is an *intrinsic automatic, periodic function* of the respective organs and is part of the widespread spontaneous periodicity of vegetative functions (Boldyreff). What are these organs? Before this question is dealt with it must be emphasized again that the fluid discharged into the duodenum in the interdigestive state is not "bladder bile" but "liver bile" mixed with the secretion of pancreas, ductal glands, and duodenal mucosa. The theory is that the liver bile is secreted without intermittence. If this is the case stoppages can only be a motor phenomenon caused by closing of the sphincter which inhibits the flow of bile into the duodenum and forces the liver bile, which according to the theory, is continuously secreted, into the gall bladder. This occurs as long as the bladder is able to receive bile. The *interperiodic stoppages of discharge into the duodenum, then, can be identified as the "filling periods of the gall bladder"*. When the gall bladder is filled and no longer able to receive bile the continuous secretion increases the intraductal pressure which opens the sphincter so that now the liver secretion is discharged into the duodenum. *The discharges into the duodenum then correspond to the "concentration periods" of the gall bladder*. As soon as the concentration provides new receptive ability of the bladder, a new filling follows and, therefore, another period of stoppage of discharge into the duodenum. The explanation of the stoppages as filling periods seems supported by the finding that the stoppages are well marked in individuals with gall bladders and less marked or missing when the gall bladder is absent.

There is, however, some conjecture as to whether the stoppages of discharge are exclusively filling periods of the gall bladder or whether part of them is due to physiological intraductal retention of bile or to physiological intermittence of liver secretion. Lantieri space does not make possible a thorough discussion of this problem but a few hints may characterize it. The theory is deduced from unintermittent flow of bile from drains in the common duct. However, unintermittent flow from an open drain in the common duct does not

exclude the possibility that the liver would secrete intermittently when acting under the influence of the naturally closed system including the activity of the sphincter of Oddi since then there is a possibility of pressure reflexes emanating from the bile ducts to the liver which are entirely missing in open drainage from the common duct. Moreover it may be assumed from roentgenologic cholecystograms that at the time when the stoppages of discharge into the duodenum were established, that is after a fourteen hour fast, the limit of capacity and concentration in the gall bladder is reached so that the gall bladder does not take on further bile. It seems doubtful, therefore, that it is exclusively the filling mechanism which causes the stoppages of discharge. In support of this assumption it has been shown experimentally that a stoppage can be produced without interference of gall bladder filling (figure 2).

A patient had a T-tube drain in the common duct for six months because of a stenosis of the common duct, the liver function was normal and the general condition was fair. The flow of bile from the common duct was recorded for five successive hours and found uninterrupted, so long

as the intraductal pressure was kept negative by slight syphonage or at least below plus 15 cm. of water. Elevating the outflow end of the drain 15 cm. above the level of the common duct stopped the flow from the common duct drain for about thirty minutes, without substituting discharge into the duodenum as checked by duodenal tube. Thus, there was a stoppage of discharge for which moderate increase of intraductal pressure and not a filling period of the gall bladder was responsible. Only two mechanisms are possible: continued secretion into gradually dilating bile ducts or real stoppage of liver output.

RHYTHMICITY

The prolonged quantitative drainages revealed an outspoken rhythmicity of the volume of discharge as a regular phenomenon. During the periods of discharge the drainage output and, therefore, the discharge of duodenal content comes in waves i. e. the amount per five minutes increases and decreases rhythmically. This rhythm is most marked when the discharge is ample (figure 3) and during the long periods of discharge

of the "non-stop type." However, it is indicated also in the "medium stop type" and "long stop type," although in a less marked and regular form.

How does this rhythm of discharge volume come about? Is it due to rhythms of sphincter or rhythms of the liver output? It could be established that it is a primary rhythm of the liver output, accommodated and modified by secondary rhythms of the sphincter activity. Proof was obtained in the patient who had a T-tube drain in the common duct for six months. Here the output of the liver itself presented quite a similar rhythm (figure 2) when the liver bile was collected directly from the common duct under elimination of sphincter action. The objection that intermittent escape of bile through the sphincter produced this rhythm of the discharge from the common duct was ruled out by a drain in the duodenum which showed that at the

trough of the waves there were no rhythmic escapes into the duodenum. Thus the rhythm of the discharge volume is not simply due to a rhythmical widening and narrowing of the sphincter of Oddi but to a rhythm of the secretion itself and to eventually associated tonus rhythms of the extra-hepatic and intrahepatic bile ducts. One could imagine

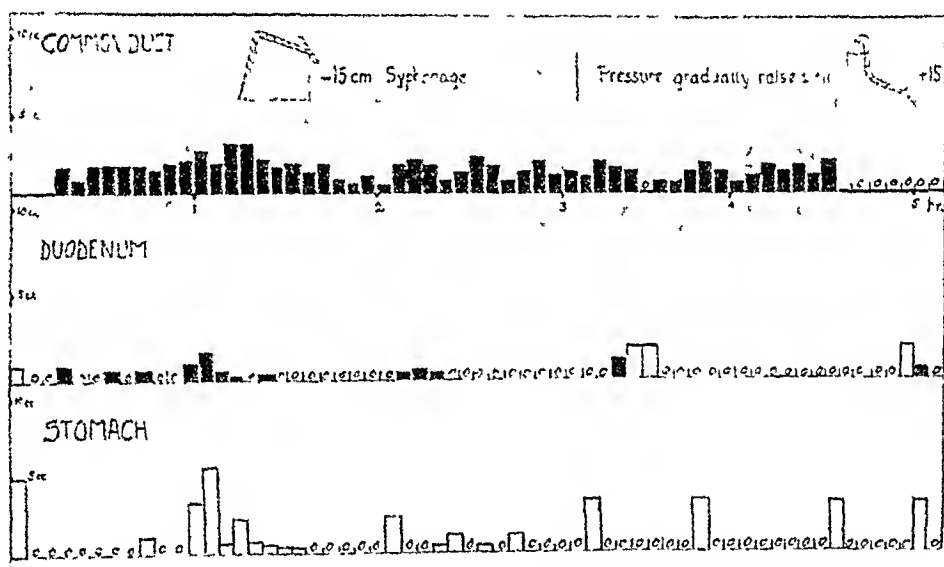


FIGURE 2.

Rhythmicity of Discharge of Liver Bile from the Common Duct as Proof of the Hepatic Origin of the Rhythm. Uninterrupted Discharge at Low Common Duct Pressure Throughout Five Hours; Stoppage after Moderate Increase of Intraductal Pressure.

that an intensification of the negative phases of this secretory rhythm may result in real interruption of secretion and this might occur in the intact system: "liver-ducts-sphincter" so that periodicity of discharge into the duodenum could be caused not only by a filling period of the gall bladder but also by actual interruption of secretion owing to an intensification of the rhythm of the discharge volume.

AMOUNTS OF DISCHARGE

The third of these investigations concerned the amount of the interdigestive discharge into the duodenum. It was demonstrated that marked pathological variations of amount exist. In thirty prolonged quantitative drainages, the following amounts of duodenal content were obtained: 10-25 cc. as average per hour, maximally 50 cc. per hour. The maximal output per five minutes was 6-10 cc., sometimes about 15 cc. In two cases of liver cirrhosis analysed by means of six quantitative drainages extreme and continuous hypersecretion was found (figure 3). The upper row of the

figure gives a picture of such hypersecretion in a patient with liver cirrhosis, the lower row for comparison, an average discharge in a patient with uncomplicated cholecystectomy. The total amounts per hour were 192 cc. and 28 cc. respectively. The hypersecretion lasted as long as the drainage was done, that is, at least five hours producing 860 cc. per five hours in the patient with liver cirrhosis, whereas the other patient produced 140 cc. per five hours. The hypersecretion was probably continuous, because in one patient who could be drained several times during a one year period, the hypersecretion was shown at every successive drainage and throughout the whole drainage.

concerned. At present, the finding of a marked hypersecretion of duodenal content in cases of liver cirrhosis substantiates the value of quantitative examination of duodenal content.

SUMMARY

The present investigations show that quantitative studies of interdigestive discharge of duodenal content in man are possible and worthwhile. They offer facts of clinical value and contribute to the physiology of the important but rather neglected field of interdigestive functions. In general, they indicate that oscillations of this discharge are not pure motor phenomena but

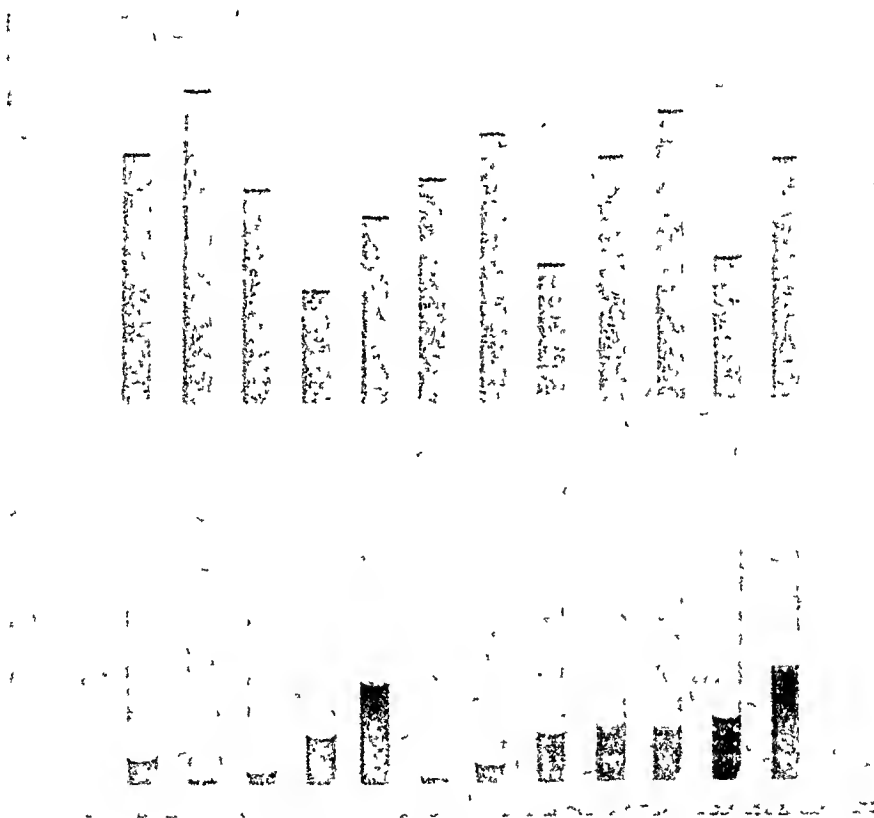


FIGURE 3.
Hypersecretion of Duodenal Content in Liver Cirrhosis (192 cc. per hour.) Normal Amounts in an Uncomplicated case of Cholecystectomy (28 cc. per hour.)

The concentration of the fluid was very low. A thirty-six hour thirst and in the patient with ascites, a very pronounced dehydration, a loss of 22 pounds of water within forty-eight hours, did not eliminate the hypersecretion only reduced it moderately. Of the patients with hypersecretion of duodenal content one had a non-aseptic cirrhosis, the other an ascitic cirrhosis. The first explanation of the increase of duodenal content would be pathologic transudation of the duodenal mucosa and caused by portal obstruction. Such transudation however, was not found in the stomach in which the same circulatory disorder may be assumed. The second explanation would be a secretory dysfunction of the cirrhotic liver and pancreas similar to that in nephrosclerosis. Further studies are necessary as far as mechanism and consequence of this finding are

are due to an intricate motor and secretory synergy of all the systems involved.

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Notes on Nutrition

Heat production and heat loss. "It may be asked if nutrition as a discipline should try to cover a wide field with outlying areas that may belong in part to physiology or biophysics. Nutrition cannot afford to abandon territory that belonged to it in the great period of its development. It must include not only the study of heat production and heat elimination but also intermediary metabolism, tissue metabolism and a great deal of biochemistry as well as food economics. If it neglects these border zones it may become so narrow that it will have to change its name to dietetics." The chief product of oxidation, viz., heat and energy, usually is overlooked. We do not know exactly what effects clothing has on problems of nutrition, especially heat production and elimination. We know little about internal temperature. The body has many temperatures. How many students realize that most of our athletic records are made by men with fever temperatures caused by the discrepancy between heat production and heat loss? (Eugene F. DuBois, Dept. of Physiology, Cornell University Medical School, New York, N. Y.)

Histopathology of skin in avitaminosis A. Cutaneous lesions observed in China were attributed to lack of vitamin A, and similar observations were made in India, the chief characteristic being the formation of keratotic plugs in the hair follicles with a rough dry skin ("toad skin," "nutmeg grater skin"). Now a careful experimental investigation (Arch. Dermat. Syph. 47, 768, 1943) on rats supports these clinical investigations, for it showed that as the amount of vitamin A in the diet was reduced from 50 IU daily to zero per day, there was increasing keratinization of the skin, with decreasing hair follicles, and finally overdistension of follicles with keratin or actual plug formation.

Peculiarities of ruminant nutrition. In the calf the first three of the four compartment stomachs are small and the fourth large, but later in maturity, the first three (rumen) enlarge and the fourth remains unchanged. The rumen has no secretory action, all changes in food and roughage being due to the activity of bacteria through fermentation. Ruminants can live on cereal concentrates indefinitely but they must be fed often in small amounts to prevent bloating. Gases formed are carbon dioxide and air. Most of the members of vitamin B complex are synthesized in the rumen. Ascorbic acid is apparently not synthesized in the rumen but in the tissues of the body. Vitamins A, D and E must be furnished the ruminant in the feed. Urea can be synthesized into protein by microorganisms. It is only when urea and ammonium salts replace a part of the protein in rations incapable of maintaining nitrogen equilibrium, that positive results are obtained. The ruminant is able to extract about 30 per cent of energy available in roughage (J. Animal Sci., 1, 236, 1942) (Nutrition Abstract and Review, 12, 531, 1943).

Correlation of dietary findings with nutritional status. A "diet score" method of checking the diets of a large group of girls and boys in Canada, was used and then the subjects were physically examined for evidence of specific food element deficiencies. The striking fact about the results was that no correlation could be shown to exist between the diets as recorded and the physical status of subjects as determined. (Canad. J. Pub. Health, 34, 193, 1943). Dietary surveys do not by themselves provide a direct and accurate measure of the prevalence of malnutrition. The field is complicated by the many tests needed and there is a shortage of clinical examiners trained in modern techniques of studying nutritional deficiency diseases of the milder sorts.

The nutritive value of dehydrated vegetables. The preservation of vitamins during dehydration and storage of vegetables is a complex problem. Ascorbic acid is most easily destroyed, but if temperatures are kept below 70 degrees C, there is fair retention. Most of the factors of vitamin B complex stand the process fairly well. The precise fate of vitamin A, under the processes of dehydration, and in the case of various vegetables, is a moot question and conflicting reports have been made. Possibly the civil population will care little for dehydrated foods after the war because of flavor changes, but the problems are urgent in wartime feeding of the armed forces. (J. Am. Dietet. Assn., 19, 13, 1943).

Experimental manganese deficiency. The most recent study of manganese deficiency in rats and mice indicate that manganese is necessary for the production of viable young. In the least severe stage, the deficient female gives birth to viable young which develop symptoms of ataxia and poor equilibrium. In the second stage, nonviable young are born. In the most severe depletion, the estrus cycle is disturbed and sterility results (J. Nutrition, 26, 1, 1943).

Diet and stomach lesions. By means of various deficient diets, gastric ulceration can be produced in rats in high percentages. It has been found that choline when added to some of these diets greatly reduces the incidence of lesions, and it is to be assumed that choline is of importance in preventing ulcerous lesions in the forestomachs of rats (Cancer Research, 3, 108, 1943) (J. Nutrition, 25, 113, 1943).

Protein metabolism and the vitamin B-complex. From many experiments undertaken to elucidate the relationship between members of the vitamin B-complex and the protein metabolism, it may, at this time, be concluded that some of the components of the vitamin B-complex have a favorable effect on protein anabolism; that protein seems to spare thiamine; that protein deposition may be necessary for the retention of riboflavin and niacin by the liver and that a creatinuria develops during deficiencies of thiamine, riboflavin, pyridoxine and pantothenic acid presumably because of the attendant protein catabolism. (Nutrition Reviews, 1, 172, 1943).

Tyrosine poisoning in rats. Feeding rats 10 parts of levo-tyrosine in place of an equivalent amount of sucrose, making a total of 11.17 parts of tyrosine in the diet, led to rapid and marked degeneration and necrosis affecting many organs and markedly damaging the blood vessels. The most striking effects were seen in the pancreas (Arch. Path. 35, 685, 1943).

The microbiological determination of riboflavin. As cereal products, meat and milk are among the major sources of riboflavin in the American diet, the new data on riboflavin assays are of special interest to those concerned with the appraisal of the riboflavin content of the diet and its correlation with laboratory and clinical findings (J. Nutrition, 25, 143, 1943).

Geographic factors and vegetable nutrients. A study of the synthesis of ascorbic acid in turnip leaves shows that "place" has a marked effect on the yield. The amount of ascorbic acid expressed in mg. per gram of leaves, shows that in Norfolk, Va., it was 2.41, in Blacksburg, Va., 1.28, in Stillwater, Oklahoma, 1.59, and in Experiment, Ga., 1.91. The use of potassium treatment gave lowered yield in Georgia especially. Many of the factors which one would imagine important, such as soil composition, temperature, rainfall, etc., did not seem nearly as important as "place," although no one yet knows why this should be so (J. Agr. Research, 66, 375, 1943).

Thiamine inactivation by raw fish. Raw fish contains a factor, probably a protein, with enzymatic activity which destroys thiamine. If the diet of foxes contains as much as 10 per cent or more of raw fish, the foxes contract a form of paralysis, believed due to lack of thiamine and resembling Wernicke's Disease in man, and known as Chastek's disease. An active form of this factor can be prepared in the form of tissue powder by drying the acetone-defatted tissue over phosphorus pentoxide (J. Am. Chem. Soc., 65, 935, 1943). About half the fresh water fish examined contain this factor although none of a series of 9 salt water fish examined contained it. It may be of value in removing thiamine from an experimental diet.

Eating under war conditions. How can we obtain our supply of protein with meat rationing? Through meat tickets, allowing for bone, one can get about 24 gms. of protein a day, which is one-third of the protein intake recommended by the Food and Nutrition Board. The difference can be made up by using unrationed meats, fish, cheese, milk, vegetables, peas, lentils, peanuts and cooked cereals. (New England J. Med., 228, 809, 1943).

Stability of carotene in fortified foods. It was found that hydroquinone was effective in retarding carotene destruction by oxidation, when the carotene was dissolved in oils. Corn oil itself contains anti-oxidative factors. Alfalfa concentrate contains great antioxidant properties. Crisco and oleomargarine are superior to lard in their content of natural antioxidants (Ind. Eng. Chem., 35, 794, 1943).

Relationship between vitamin B-complex intake and fatigue. Recent well-controlled work (J. A. M. A., 122, 717, 1943) shows even more convincingly than some past work by others, that the result of vitamin B

deficiency actually does cause fatigue, irritability, lack of energy, anorexia and increased leg pains. In this experiment the subjects were not told the nature of their diet, so the psychological factor was avoided. While the urinary excretion of thiamine and riboflavin dropped to low levels during the deprivation, there were no physical signs of disease. Restoring vit. B to the diet restored the normal energy and working power.

Increased erythrocyte destruction on a high fat diet. Experiments show that high fat feeding does cause increased blood destruction, presumably by hemolysis in the portal circulation, as evidenced by increased excretion of bile pigments. This may be a normal form of blood destruction in the dog, but no anemia results because the hemopoietic tissues are constantly able to make good the losses (Am. J. Physiol., 138, 230, 1943).

Effect of carrots on the resistance of rats to acute anoxia. Carrot diet causes rats to survive periods of oxygen lack under reduced barometric pressures which promptly kill rats not so fed. Thus far it is thought that the virtue of carrots in this regard depends on four factors, (1) low protein content, (2) presence of fiber, (3) presence of glutamine, (4) an unknown factor. This work is very interesting but as yet cannot be said to have solved certain urgent problems in aviation. (Proc. Soc. Exp. Biol. Med., 52, 1, 1943).

Metabolism of zinc. Zinc is essential for the growth of rats and must be required for man since it is a constituent of carbonic anhydrase. The usual human daily intake is 15 mg. Most is excreted by the bowel, very little by the kidneys. Increasing the intake does not increase the urinary excretion of zinc. In patients with albuminuria, there is a marked increase in the urinary excretion of zinc. Such individuals are thought to be suffering from a zinc deficiency, but the symptoms of such a deficiency are unknown. Zinc after ingestion or injection is rapidly deposited in the liver. Zinc appears necessary for the storage of insulin in the pancreas. The evidence indicates that the zinc of the body is widely distributed and is probably associated with proteins, at least some of which are enzyme molecules (J. Biol. Chem., 149, 139, 1943).

Pantothenic acid and reproduction. It has been tested in experiments on hens, chick embryos and on mice that the use of excessive amounts of pantothenic acid, beyond nutritional needs, has the effect of increasing the rate of reproduction. Increasing the amount of this substance available to developing chick embryos led to a greater hatchability of eggs. Rats showed from 21 to 27 per cent increase in the size of litters. The brains of such offspring are 14 per cent underweight. Pantothenic acid seems to increase the survival of fertilized eggs. Here, then, is one vitamin at least which has a physiological effect in large doses which is not shown by the amount necessary to maintain health. (Am. J. Physiol., 139, 183, 1943) (Am. J. Physiol., 137, 527, 1942).

Vitamin E and neuromuscular regeneration. It was found that while tocopherol is effective in preventing muscle regeneration due to vitamin A deficiency, if

given early enough, that the supplementing of diets with vitamin E did not assist in neuromuscular regeneration following a mechanical injury to the nerve (Am. J. Physiol., 139, 183, 1943).

Maternal nutrition as related to pregnancy and fetal development. The effect of maternal nutrition on the course of pregnancy and labor has received considerable emphasis during recent months (Nutrition Reviews 1, 276, 1943). Attention has been given to the relationship of diet to the occurrence of polyneuritis, the frequency of anemia during pregnancy, and the character of labor. There has been less adequate analysis of the effects of maternal nutrition on the health of the fetus even though Hart, McCollum, Steenbock, and Humphrey (Res. Bull. no. 17, Wis. Agr. Exp. Sta., 1911) many years ago pointed out that the diet of heifers seriously affected the viability and vigor of calves, and Warkany (Nutrition Reviews 1, 207, 1943) more recently has demonstrated that the diet fed to breeding female rats influenced the incidence of congenital abnormalities in their offspring. Of great interest, therefore, is the report by Burke, Beal, Kirkwood, and Stuart (Am. J. Obst. Gyn. 46, 38, 1943) of a long study of the effect of maternal nutrition on fetal development and infant health as well as on the complications of pregnancy.

The women selected for the investigation were patients in the prenatal clinics of the Boston Lying-in Hospital. They were examined at frequent intervals throughout pregnancy and careful dietary analyses were made. Diets were called optimal if they provided daily 2600 to 2800 calories, 85 to 100 g. of protein, 1.5 g. calcium, 2.0 g. phosphorus, 20 mg. iron, 8000 I.U. vitamin A, 2.0 mg. thiamine, 2.5 mg. riboflavin, 18 mg. niacin, 100 mg. ascorbic acid, and 400 to 800 I.U. vitamin D. A rating of "excellent" was assigned to those diets which contained these "optimal" amounts of foodstuff, "good" if they had 80 per cent or more, "fair" if they contained 60 per cent to less than 80 per cent, "poor" if they provided less than 60 per cent, and "very poor" if they contained less than 50 per cent. The observations reported were obtained on 216 women and their infants. The majority of the families represented had weekly incomes of \$25 to \$40. About 70 per cent of the women were under the age of 30 years.

A statistically significant relationship was found to exist between the adequacy of the maternal diet and the course of pregnancy. Of the women with "good" or "excellent" diets, 68 per cent had a normal prenatal course, while of the women with "poor" to "very poor" diets, only 42 per cent had a normal prenatal course. Furthermore, no instance of preeclampsia occurred in those women whose diets were "good" or "excellent," but almost 50 per cent of the mothers whose diets were "poor" to "very poor" had toxemia. No statistically valid correlation could be made between the untrifling adequacy of diets consumed and length and character of labor or the over-all complications of labor and delivery. Mothers whose diets were "poor" to "very poor" tended to have more difficult types of labor and more major complications at deliv-

ery despite the fact that they had, on the average, smaller infants than were born to the women in the "good" or "excellent" diet group. There was a tendency for a relationship to exist between prenatal nutrition and major complications of the postpartum period, but the relationship was not definite or distinct.

The influence of maternal diet on the condition of the infants was striking. Mothers whose nutrition was "good" or "excellent" gave birth to children with pediatric ratings as follows: 42 per cent "superior," 55 per cent with one or two minor physical defects, and 3 per cent with congenital defects. On the other hand, infants born of mothers on "poor" to "very poor" diets were rated: 2.5 per cent "superior," 2.5 per cent with one minor physical defect, 28 per cent in fair or poor general condition, and 67 per cent in "poorest" condition. This latter group consisted of infants who were stillborn, who died within a few hours or days, had marked congenital malformations at birth, were premature (under 5 pounds at birth), or were "functionally immature." The size of the infants was equally striking. Those born of mothers with the best diets had an average weight of 8 pounds 8 ounces and an average length of 20.4 inches; those born of mothers with inadequate diets averaged only 5 pounds 13 ounces in weight and 18.6 inches in length. In only one instance did a mother whose nutrition was good give birth to an infant in poor physical condition.

This correlation was made on the basis of maternal nutrition as related to the condition of the infant. If the process is reversed and the condition of the infant at birth is correlated with the adequacy of the maternal diet, the results are equally convincing. The "superior" infants were produced by mothers whose diets had the following percentage distribution: "good" or "excellent" 56, "fair" 35, and "poor" to "very poor" 9. In contrast, when the condition of the "poorest" infants was studied in relation to the prenatal nutrition, it was found that 79 per cent of the mothers had diets which were rated as "poor" to "very poor," 18 per cent had "fair," and only 3 per cent had "good" or "excellent" diets.

From these results it appears that poor nutrition during pregnancy affects the fetus more profoundly than it does the maternal organism. This is contrary to the usual obstetric teaching, and should certainly give both direction and impetus to the prenatal health program now spreading throughout the nation. The authors state that the physical status of the women during pregnancy was evaluated and, since the study was painstakingly done, it is probably safe to assume that women selected for the investigation suffered no evident impairment of health other than the conditions listed. The critical reader, however, would like to have had additional data in regard to the nutritional status of the women during pregnancy, namely hemoglobin and red blood cell count, serum proteins, and plasma ascorbic acid, which might have added to the validity of the dietary histories.

Editorial

PLEASE RECORD YOUR HOBBY

TEN years is old for a *new* medical journal. This journal will be ten years old in March 1944. It is no longer new. Like men who have reached a tolerable age, it is wondering about,—*hobbies*. So the Journal will celebrate by starting a new section soon, to deal with that important subject,—what medical men do for fun.

Although doctors are bashful and hate publicity, we feel that they ought to overcome these commendable qualities since it is all amongst ourselves. Why not tell the medical world about your own hobby? We understand that you started it, not for publicity purposes but for your innate liking of it. Nevertheless, it would be of great interest for the reading medical public to know just what you do when you are working at it.

We know that hobbies are good for spastic colons and nervous indigestion, so long as the hobby does not get too burdensome. Probably you have prescribed hobbies for persons with coronary diseases or melan-

cholia or private frustrations. We all agree that doctors are somewhat prone to some of these afflictions, which are made worse by the times,—war, work, loss of sleep, high taxes, and medical manpower shortage. Maybe we all ought to have hobbies.

The new section will begin as soon as manuscripts arrive in quantities. They may be long or short and may be accompanied by photos. If you know of a doctor friend who has an interesting hobby, why not write him up, or persuade him to do it himself?

Every medical journal has a little extra space that yawns for a filler. Medical jokes are good, but they are all old. Medical hobbies have not yet been overdone. Some doctors excel at painting, because they know anatomy. Some of them write excellent poetry because they know life. Many of them fly because they don't like it on the ground. Many make queer gadgets, for no reason whatever. Whatever you do, we shall indeed be grateful if you will write yourself up for our new section.

Book Reviews

A Hundred Years of Medicine By C. D. Haagensen and Wyndham E. B. Lloyd. Sheridan House Inc., New York (\$3.75) 1943.

As the title implies, this book is a brief history of medicine during the past hundred years. The present American edition apparently differs in several respects from the original English version by Dr. Lloyd; features peculiar to the American scene have been added and some especially English details omitted. The first nine chapters are devoted to medical history before the eighteenth century. The theories prevalent at the time, the practice of healing and surgery, the conditions of hospitals, and medical education are covered, briefly but interestingly. Twenty-six chapters are devoted to medical science and surgery during the last hundred years and two chapters are given to a glance into the future.

The volume lacks the crusading style of other quasi-popular histories of medicine and thereby probably gains in its value. It covers aspects of medicine which most books miss, aspects chiefly of a social and economic bearing.

The book is written authoritatively and in an extremely fine style and holds attention throughout. It may be recommended by the physician to those of his patients who sometimes express an interest in medicine and wish to know something about its background. It should make a fine gift to a student about to commence his medical studies. It will repay reading.

Microscopic Technique in Biology and Medicine. By E. V. Cowdry. pp. 206. (\$4.00). Baltimore, Williams and Wilkins, 1943.

In his preface, Professor Cowdry characterizes this book as a brief entree to microscopic technique. However, close inspection of the book will prove it to be much more than that. The purpose of the book was to "extend the horizon by exposing . . . a few of the many opportunities awaiting workers . . . interested in the minute structure of things." The opportunities certainly appear to be many. The old microscopic method of cutting a tissue, staining and examining it constitutes only one of the procedures now available. Ultra-centrifugation, ultra-filtration, micro-dissection, micro-incineration, tissue culture, etc., are but a few of the modern methods designed to further our knowledge of the minute structure of things. While most of these at present are still confined to research use, many are entering daily the field of "routine analyses."

The reader will find it a concise dictionary of practical methods and a source book of much recent bibliography. The subjects covered range from a bibliographic reference to the A-V. Bundle and a discussion of acid-fast bacilli to the formula for Zenker's fluid and a description of zymogen granules. This slim book should prove of great value to the research worker and technician alike. It is heartily recommended.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

KAY, E. B.: *Observations on reconstructive intra-thoracic oesophagogastric anastomosis following resection of the oesophagus for carcinoma.* (Surg. Gyn. Obst., V. 76, P. 300, February, 1943.)

It is the opinion of the author that 40% of the esophageal carcinomas present operable lesions. The problem, however, presents serious anatomical obstacles: the lack of peritoneal covering, the meager blood supply of the esophagus, the longitudinal coat of muscle, its high degree of fixation, and the vital relations of the tube. This is superimposed on the usual emaciation and avitaminotic state of the patient. The bacterial flora and stasis of food increase the surgical hazards. The usual operative procedures employed are: gastrostomy, with or without retrograde radium implantation, irradiation, and esophagectomy. These rate mortalities of from 31% to 70.6%.

The author presents the results of experiments with three other procedures (1) Reconstructive antethoracic esophagogastric anastomosis, (2) Reconstructive intra-thoracic esophagojejuno-gastric anastomosis, (3) Reconstructive intrathoracic esophagogastric anastomosis. The last of these is still in the experimental stage, the second is palliative in nature and recommended when the others are not feasible (as in very high neoplasms).

The intrathoracic esophagogastric anastomosis has, however, already been used in humans, and the author reports 4 successful esophageal and gastric resections with esophagogastric anastomosis. The operation is done in two stages. In the first, a gastric tube is made from the greater curvature of the stomach, maintaining of course its blood supply, divided at the pylorus transversely, pushed thru the diaphragm and sutured. In stage 2, performed 7-10 days later, any rib may be cut, and the gastric tube anastomosed to the esophageal segment. This was tried in 12 dogs, only three of which died thru disruption of the anastomosis.

The author states: "The technique of the transpleural partial gastric resection and resection of the distal end of the esophagus and esophagogastric anastomosis for carcinoma of the cardia of the stomach fulfills all the principles for a sound surgical operation. . . . There is an excellent exposure. . . . The regional lymph nodes can be included in the resection. . . . the oesophagogastric continuity is restored, so that the patient may eat normally."—J. L. Garcia-Oller.

STOMACH

HELD, I. W. AND BUSCH, I.: *Cancer of the stomach: with special reference to early diagnosis.* (Ann. Int. Med., V. 18, P. 719, May, 1943.)

The practical importance of the fact that only 30 to 40% of resectable cancers of the stomach are submitted to the surgeon obviously lies in diagnosis. With this thought in mind the authors discuss the present day means at our disposal. In addition to roentgenology the increased importance of gastroscopic examination is emphasized. Because of the different sites of involvement, normal acidity and negative physical examination should not influence the diagnosis. Though subjective symptoms, especially when a silent area of the stomach is involved, are vague the history is probably the most important single factor which leads to X-ray and gastroscopic studies.

All cancer of the stomach might be preliminarily placed into two groups (1) cases which develop on a previously healthy mucous membrane, and (2) cases which develop on a previously diseased mucous membrane. The former consists of about 70% of the cases. In the first group it is necessary to consider separately involvement of the posterior wall, the lesser curvature, the anterior and posterior walls, the pyloric region, the prepyloric region, the cardia, and the entire stomach (limitis plastica) with regard to peculiar symptoms and signs, Roentgen ray findings, and gastroscopic evidence. For the most part the cancer is slow growing and late in metastasizing; in such cases surgery is indicated in spite of a marked secondary anemia. Two types of rapid growing early metastasizing carcinoma, (1) the medullary form and (2) the small hazel nut size which spreads to lung and brain before gastric symptoms are manifested, can be treated only palliatively if surgery is to be done at all.

In the remaining 30% the diseased mucous membrane is one of gastritis, polyposis or gastric ulcer. Of the ulcer group there are cases in which the ulcer actually precedes the cancer and cases where the cancer begins with ulcer symptoms without the presence of ulcer. These are considered separately. If the anemia is hypochromic, iron and blood transfusions are beneficial; if it is hyperchromic (often associated with achylia gastrica) liver extract in addition is indicated. —E. D. Knerr, Jr.

malformation of the entire pancreatic exocrine system was the basic lesion. The islets of Langerhans were normal.

Other cases reported have been clinically similar. However, the pancreatic pathology has been either one of obstruction of the larger pancreatic duct or atresia of the pancreatic duct system with dilatation or cyst formation of the ducts, ductules and acini. One case has been described in which the pancreas was normal but in which biliary cirrhosis and incomplete development of the larger hepatic biliary ducts created the main picture.

It was concluded that normal meconium requires pancreatic enzymes as well as bile for the maintenance of its normal composition and consistency. A lack of pancreatic enzymes results in failure of digestion of fats and proteins, inspissation, accumulation in the intestines since peristalsis cannot dislodge it, and fatal intestinal obstruction.—F. D. Knerr, Jr.

HOLLOWAY, J. W.: *Regional ileitis*. (*Ann. Surg.*, V. 118, P. 329, Sept., 1943.)

The author presents a series of 13 cases of regional ileitis which outline the possible sequence of events in gross pathology of the disease. He divides the stages clinically into acute, subacute, chronic forms.

Acute forms show sharp demarcation, sponge rubber-like consistency, marked edema which varies from white to pink, enlargement of the mesenteric nodes of the involved segment, with accumulation of intra-abdominal fluid. There is absence of local inflammatory signs, but there is evidence of lymphatic blockage.

The subacute forms show the sharp demarcation and spongy consistency, but there is a desquamation of mucosa, which may be complete, with replacement by a hemorrhagic exudate with engorgement, producing the fiery red appearance of the lesion as seen through the normal peritoneum. At operation, it may resemble strangulation or embolic phenomenon. The bowel is friable, and so is prone to perforation with fistula formation. This stage continues into stenotic or fistula stage, in which there is little possibility of spontaneous subsidence.

The chronic forms show a thickening, rigidity, and tumor formation which is due to developing adhesions between adjoining loops or extensive inflammatory reaction in adjacent mesenteric nodes. The mucosa is extensively ulcerated, with the ulcers varying in depth and being distributed along the mesenteric border of the intestine. There are areas in which the lumen is markedly decreased.

X-ray diagnosis is of value only in the chronic stage with its "string-sign." Acute forms may subside completely or become subclinical; but resection or ileocolostomy with exclusion is the operation of choice with the chronic types. Friability with tendency to perforate in the subacute stage contraindicates operation.—Ivan F. Bennett.

RYLE, J. A.: *Rectal pain*. (*Guy's Hosp. Reports*, V. 91, P. 147, 1942.)

As compared with the insensitivity of the rectal

mucosa to stimuli, the ano-rectal mucosa is very sensitive, especially its lower portion where the exquisite sensibility is associated with great muscular force which resists distention. Severity of pain in an hollow organ has been shown to be inversely proportional to its distensibility. The discriminating ability of the ano-rectal mucosa is seen in the distinction between presence of flatus and feces as compared to formed and fluid stools at defecation.

Rectal pain may be caused by several mechanisms. There is a direct irritation of exposed nerve endings in anal ulcers and fissures with referred pain and absence of lesions. With diarrhea or dysentery with tenesmus, there is a stimulation of the anal mucosa by distention, resulting in a local pain which is burning and fluctuating in intensity with variations in sphincteric action; this is of mucosal rather than muscular origin and so can be compared to the esophageal sensations of "heat-burns." Rectal carcinoma causes pain late in its course, and then by extension to neighboring structures; more constant early symptoms are frequency, urgency, looseness and melena. Pain may be caused by excessive peristalsis as in ball-valve accumulations of hard feces giving a "bearing down" pain as in labor. Rectal spasm (nervous proctalgia) is a functional disturbance producing a dull "rectal toothache" pain, giving the impression that the sacrum or coccyx is being pushed forward or backwards; in this pain, the causative agent is probably in the recto-coccygeal muscle fibers which are involved in a spasm. The spasm can be overcome by distention of the rectum with air or water. This is the purest type of rectal pain, coming as it does "out of the blue" without complications being present. It is frequently associated with fatigue, over-work, anxiety, or sexual excitation.—Ivan F. Bennett

MORLOCK, C. G., AND GRAY, H. K.: *Congenital duodenal obstruction*. (*Ann. Surg.*, V. 118, P. 372, Sept., 1943.)

The authors give a brief review of the causes, symptoms, and diagnosis of congenital duodenal obstruction; and they report on a case in a girl of sixteen.

The congenital condition is rare among adults, though acquired duodenal obstruction is a common complication of duodenal ulcers. The lumen may be occluded from within by atresia or septum; or from without by malrotation, or by annular pancreas, or by cysts from the liver, mesentery or pancreas. Death occurs shortly after birth if the obstruction is complete; if partial, adulthood may be attained, though, usually, with lack of normal development.

Symptoms depend on the degree of obstruction, and include vomiting, distention, and, at times, distress, duodenal succession sounds, and visible peristaltic waves. It is to be differentiated from either appendicitis or duodenal ulcer.

The case report of a 16-year old girl admitted with the chief complaint of intermittent attacks of epigastric distention followed by vomiting, precipitated especially by coarse foods. When on operation the transverse colon was retracted upwards, incomplete rotation

of the colon and invagination of the duodenum between the leaves of the ascending mesocolon were noticed. The first portion of the jejunum had herniated through an opening in the mesentery of the terminal portion of the ileum. The duodenum was markedly dilated up to this point; distal to the bowel was normal.

The obstruction, in this case, was intermittently partially relieved, permitting long intervals of freedom from the trouble. Normal development of the patient was not impeded. —Ivan F. Bennett.

HARSMANN, W.: *Arteriosclerotic aneurysm of abdominal aorta with perforation into upper jejunum.* (*Brit. Med. J.*, P. 362, Sept. 18, 1943)

The patient had a history of fibrositis of the upper abdomen, long-standing rectal and vaginal pain and, lately, an unheralded hemorrhage. The diagnosis was aneurysm of the abdominal aorta with rupture into the small intestine. The patient died and the diagnosis was confirmed at autopsy. An aneurysm, due to arteriosclerosis, was found to extend down to the bifurcation. It probably exerted pressure on the inferior mesenteric ganglion and the pain was referred to the vulva and rectum. During life the aneurysm ruptured into the jejunum through an aperture less than 5 mm. The condition is comparatively rare and diagnosis may be missed for years. —John J. Cox.

PANCREAS

ORMOND, J. K., WADSWORTH, G. H., AND MORLEY, H. V.: *Pancreatic lesions confusing urologic diagnosis: report of three cases.* (*J. Urol.*, V. 48, P. 650, Dec. 1942.)

Anatomically the pancreas is so situated retroperitoneally that its head is in close proximity to the right renal fossa and its tail to the left. Presented are three cases of pancreatic cysts which prior to operation were thought to be renal tumors. All of the instances of real confusion reported with one exception were due to cysts. These can be divided into five groups: (1) pseudocysts, (2) retention cysts, (3) neoplastic cysts, (4) cysts resulting from defective development, and (5) parasitic cysts.

Cysts are usually smooth, tense, and circumscribed; they are present most often in the upper left abdomen and are associated with pain in the left epigastrium extending into the back.

There is little likelihood of confusing acute pancreatitis, malignant tumor of the pancreas, accessory pancreas, adenoma, pancreatic lithiasis and necrosis with renal conditions.

In case 1 the complaint was a dull aching pain in the right upper quadrant and back. A non-tender mass could be felt just below the costal margin on the right. With slightly impaired liver function and other findings essentially normal a diagnosis of gall bladder disease with hepatic cirrhosis was made on the first admission.

On second admission pyelograms showed the right kidney to be displaced to the left of the mid-line with evidence of rotation and a very large tumor shadow in the right upper quadrant. A diagnosis of retroperi-

toneal tumor of kidney origin was made on this basis. At operation a large cyst was found running to the head of the pancreas.

The patient in case No. 2 presented a perinephric tumor, probably abscess-complicated, with pneumonia and mild diabetes. An x-ray of the barium filled stomach revealed, however, a large elliptical shaped deformity in the greater curvature produced by an anterior abdominal mass.

After a mass in the left flank was incised and drained it was found that there was still present the anterior mass, so that the two could not have been connected. A second incision in the mid-line in the anterior upper abdomen showed a large cyst containing similar fluid to the other and filling the lesser peritoneal cavity. Probably what happened was that the products of inflammation and degeneration of the pancreas gravitated to the left loin and, burrowing through the perirenal fat, presented upon the parietes retroperitoneally; or a close examination of the left kidney showed no break in the capsule.

Case No. 3 was operated upon for a pancreatic cyst. Post-operatively pain in the left flank radiating down across the abdomen into the left testicle developed. A second re-exploration of the cyst was done, but not until then was it certain that the kidney was not involved. The typical renal ureteral distribution of pain must have been due to pressure on the left kidney by the cyst.

Six other somewhat similar cases are cited—E. D. Kuern, Jr.

FARBER, S., SHWACHMAN, H., AND MADDOCK, C. L.: *Pancreatic function and disease in early life. I. Pancreatic enzyme activity and the celiac syndrome.* (*J. Clin. Invest.*, V. 22, P. 827, Nov., 1943.)

A series of etiologically unrelated conditions causing a similar clinical picture have recently been brought together under the term "celiac syndrome." Patients with a "pancreatic fibrosis" may exhibit this syndrome. Because of the obstructive nature of pancreatic fibrosis the enzyme content in the duodenal juice is reduced, and this is the basis of differentiation of this condition from idiopathic celiac disease, idiopathic steatorrhea, non-tropical sprue and other conditions of malnutrition. Over 150 determinations of the activity of trypsin, amylase and lipase were made on the duodenal contents of infants and children. The sticky viscid nature of the duodenal contents and the smaller volumes obtainable were also suggestive of the presence of pancreatic fibrosis.—William D. Beamer.

LIVER AND GALLBLADDER

BATTY, J. L. AND GRAY, S.: *Involvement of the liver in disease of the gallbladder.* (*Arch. Int. Med.*, V. 72, P. 176, August 1943.)

The controversial evidence of pathologists and investigators studying hepatic function in cholecystic disease led the authors to make a further study of the incidence of hepatic involvement in diseases of the gallbladder.

The colloidal gold test was used because of its marked sensitivity and because it permits of a large number of studies. The material consisted of 100 patients with proved disease of the gallbladder divided into four distinct groups: (1) patients having jaundice with infection, (2) those having jaundice without infection, (3) those having infection without jaundice and (4) those having quiescent disease of the gallbladder (no jaundice or infection).

Evidence of disease of the liver was found in 58.8% of group No. 1, in 52.5% of group No. 2, in 53.3% of group No. 3 and in 36.7% of group No. 4. The incidence of hepatic damage in relation to the duration of the symptoms was also studied, and it was found that repeated insults to the liver from recurrent jaundice, infections of the gallbladder or both increased the percentage of colloidal gold reactions to 75%, 66.6%, and 100% respectively, showing the danger of delaying surgical intervention too long. In contrast to this the fourth group showed a decrease in incidence of hepatic damage as the period of quiescent disease of the gallbladder increased.

There was a correlation between the bacterial flora of the gallbladder, the pathologic changes in the gallbladder, and the incidence of liver disease. That is, the colloidal gold test was positive in a higher percentage of those patients in whom positive cultures were obtained from the bladder and bile; and the pathogenesis in the bladder was more severe and extensive in this group as contrasted with those of negative liver function tests.

Cirrhosis of the liver was found in three, carcinoma of the gallbladder in two, and cholesterosis of the liver in one of the one hundred patients studied.—E. D. Knerr, Jr.

BACON, RALPH D.: *The fat meal: its value in cholecystography.* (Penn. Med. J., V. 47, P. 137, Nov. 1943.)

A resume of opinions expressed by radiologists (twenty from Pennsylvania and ten from outside the state) is presented, showing that there is little agreement as to the value of the fat meal study in radiographic determination of gall bladder function. In the author's group of 429 consecutive cholecystographic studies, 5 per cent exhibited poor emptying although they had concentrated well. He suspects as being poorly functioning any gall bladder which has not emptied at least 50 per cent within 3 hours after a fat meal. If the same findings are repeated in one month, and there is correlated evidence of gall bladder disturbance, the diagnosis of a poorly functioning gallbladder is strengthened. Previous writers have listed more than 50 cases of proven gall bladder disease in which the only cholecystographic abnormality was poor emptying, and the author adds 12 consecutively operated cases, of which 11 had gall bladder wall disease. The other case had preobstructive carcinoma of the distal colon and thus, perhaps, reflex interference with normal emptying.—Wm. D. Beamer.

RODEMAKER, L.: *Spontaneous rupture of the liver complicating pregnancy.* (Ann. Surg., V. 118, P. 396, Sept. 1943.)

Spontaneous rupture of the liver is a rare and exceptional condition with a poor prognosis. From the time of Vesalius to the present only 29 cases have been collected, only four of which recovered. These four cases all underwent surgery.

Of the 29 cases, one was a complication of pregnancy. It was reported in 1844. The patient died 26 hours after a normal labour and delivery. The cause was believed to have been due to a slight external trauma, and at autopsy showed two lacerations in the liver with bleeding from a torn portal vein root.

Dr. Rademaker's case is the second one reported of a spontaneous rupture of the liver complicating pregnancy and the fifth reported recovery from this condition. The patient showed a rapidly developed hypertension with some nausea and emesis, and appeared to be a toxemia. The patient went into labour and intrapartum showed signs of internal bleeding. This was thought due to a ruptured uterus and surgery was started. As what appeared to be a rent in the uterus was seen, a Porro section was done. The early diagnosis made possible an early operation which together with modern treatment for shock and hemorrhage made recovery possible.

The following were found significant in this case.

1. The Porro section was the quickest means of removal of the fetus and uterus to prevent any further bleeding from that source.

2. The fetus died as a result of hemorrhage of the mother.

3. Pleural effusion resulted from pressure of the pack on the diaphragm.

4. Prompt multiple blood and plasma transfusions are necessary to save these desperately ill patients.

In closing it is speculated whether some of those cases of death from collapse during treatment for eclampsia may not be due to undiagnosed rupture of the liver.—J. B. Bernstine.

SURGERY

CHAFFIN, R. C.: *The new type of drainage in gallbladder fields.* (Western J. Surg. Obstet. Gyn., V. 51, P. 440, Nov. 1943.)

The author describes his recently perfected method of drainage of infected areas. The apparatus consists essentially of two large bottles attached to a specially designed suction apparatus. One bottle has a tube which leads to the drainage tube while the other bottle is connected to a Levine tube for intra-gastric suction. The author's tube is illustrated. It is made of rubber and is double so that saline or Dakin's solution can enter the drainage area. The author outlines the technique in some of the more common operations in the biliary field. There are several illustrations. The author stresses the need for freeing the mind from the idea that a Penrose wick will drain an infected area. William D. Beamer.

The Treatment of Acute Gingivo-Stomatitis (Vincent)

By

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THERE is a wide divergence of opinion in the literature on the classification and treatment of acute stomatitis. These conditions are among the most frequent and troublesome of diseases to treat. While usually seen in a relatively mild form, they occasionally can become so severe as to threaten life.

The many theories of the causation of acute stomatitis is reflected in the large number of treatments suggested for this illness. The possible etiological factors were most succinctly discussed by Craig, (1) who stated that the mouth contained diverse forms of aerobic and anaerobic organisms, which readily cause, or perpetuate stomatitis when the mucous membrane is injured in any manner. The mucous membrane may be injured by agents of the specified infectious diseases, virus infections, blood dyscrasias, by the excretions of poisons such as mercury, or metabolic products as in uremia. The mucous membrane may also become unhealthy when certain nutritional factors are lacking such as iron, nicotinic acid, and ascorbic acid. Finally the buccal mucous membrane depends for its health on normal saliva and normal mucus. These secretions are markedly disturbed by the fevers and dehydration. Thus it can be seen that infection is the positive factor in each case, even though infection can occur most easily if the resistance of the tissues is low. A classification of the more frequent types of stomatitis is given in Table I.

The most common type of stomatitis, and the type to be discussed in this paper, is entitled acute gingivostomatitis or Vincent's stomatitis.

This is an acute disease, usually affecting children between the ages of one and three years, but occurring in children of any age, and adults as well. It is especially frequent in epidemic form in schools and armies. The original term, Vincent's Angina referred to a faucial lesion involving the tonsils and adjacent structures. This term has been improperly applied to the condition now under discussion. It has been suggested that Vincent's Disease be used to include both the tonsillar and the mouth localizations.

A: HISTORICAL (2)

The early history of the disease seems to show constant confusion with scurvy and diphtheria. Epidemics have been constantly described among soldiers since the wars of the French Revolution. During the last war it became markedly prevalent under the name "Trench mouth." There have been constant attempts to link the disease up with undernutrition in the older literature, and with avitaminosis in the newer studies. After the last war, it was rampant throughout Germany, but it usually selected vigorous young adults of both sexes, and was not really frequent until 1919, when the food supply was more plentiful and richer in

vitamins than the years immediately preceding. Nevertheless the avitaminosis theory has made many converts (3). It is not inferred here that stomatitis does not occur in avitaminotic states. Lack of local resistance definitely predisposes an individual to any infection. How then can one account for the improvement caused by the various forms of treatment recommended. Surely the avitaminotic state is not improved by a few daily treatments by gentian violet, nearsphenamine, hydrogen peroxide, or other local therapy. Rather it should be stated, the lack of vitamins predispose to infection with the organism causing acute infectious gingivostomatitis, but does not cause it. Recovery of patients with Vincent's disease after approximately 10 days of therapy with nicotinic acid does not establish an etiological factor, for in doing this, the patient's resistance to infection is being raised.

B: SYMPTOMATOLOGY

Whatever the etiology, acute infectious gingivostomatitis begins with fever (101-102 degrees), generalized aches and pains, restlessness and irritability, and the inability to eat food. Very soon thereafter, areas of redness are noted throughout the mouth, especially on the gums, which later ulcerate. A foul odor is a usual symptom. The patient looks and feels miserable. Gingivitis is the most constant feature of the disease. The gums become red and later a purple color, and are exceedingly tender. Black (5) states that the ulceration in these conditions never leads to destruction of tissue. In other parts of the mouth ulcerations are exceedingly frequent. It is difficult to differentiate clinically the individual lesions from "aphthous stomatitis," but differentiation by the entire clinical picture is usually possible. The tongue, as well as the lips, may show the ulcerations in some patients. Most of the cases present involvement of the regional lymph nodes, submaxillary, submental or both.

If to this pitiful state is added involvement of the tonsils, the full picture of Vincent's disease is seen. Sometimes the disease starts with involvement of the tonsils, which later extends to the gums and mouth structures. A student of this disease (5) feels that acute infectious gingivostomatitis and aphthous stomatitis have the same cause. The most carefully studied cases of aphthous stomatitis reveal *Oidia albicans* or some closely related fungus as the cause. In fact, it has recently been shown that aphthous stomatitis may be diagnosed before the appearance of a typical lesion by swabbing the mouth and discovering the fungus. However, it might be stated that the term aphthous stomatitis might be applied to different conditions by different observers.

C. TREATMENT

The best results are obtained in acute infectious gingivostomatitis by considering it as a distinctly infectious disease. Thus the subject should use separate water glasses, dishes, knives and forks. These dishes must also be sterilized separately. He should also use separate towels and soap. The saliva and mucus from the mouth of the patient should be disinfected before disposal. All articles that are used during the illness should be discarded on recovery.

During the acute stage, the subject will find it very difficult to eat because of the severe pain. Before attempting to eat he should suck on one of the anesthetic lozenges, e. g., anaesthesin-calcidin, troches, nuporal lozenges, or other similar pastilles. Following this, juices can usually be taken without severe pain. Smoking and alcoholic beverages are interdicted during the acute stage, as are all spicy and rich foods. An extremely simple diet, with plenty of diluted fruit juices, are the foods allowed during the acute stage.

The medical treatments recommended for acute infectious gingivostomatitis (Vincent's stomatitis) and Vincent's Angina are legion. Local applications of gentian violet, (6) bismuth violet, (7) chronic acid, (4) local and intramuscular use of neoarsphenamine, (8) bismuth, fuadin (9) (an antimony preparation originally used for Schistosomiasis) are among the substances used.

In 1941 the author (10) described the treatment of a severe case of Vincent's Angina with a sulfonamide derivative (neoprontosil) both by the oral route and by local application of a neoprontosil solution, made by dissolving a half tablet of the substance in one ounce of distilled water. At that time, he had no knowledge of an article by Lane and Vinson (11) on local use of sulfanilamide powder on two cases of a very severe form of stomatitis. More recently, Suranyi (12) noted favorable results in both Vincent's stomatitis and aphthous stomatitis by the local application of sulfonamide powders. No credit is given to either of the previous authors in this latter article.

Since then, five additional adult cases of severe Vincent's Angina and stomatitis were treated. In all these cases, neoprontosil, (a sulfonamide derivative) was used both by the oral route and by local application. Sixty grams were given on the first and second days, 45 grains on the third, and 30 grains on the fourth day. In addition, a solution of neoprontosil was made up by dissolving a tablet (5 grains) of neoprontosil in one half ounce each of distilled water and glycerin. Applications were made to the lesions of the mouth and palate if involved, every two hours. In these cases, no other medications were given, except saline irrigations which were useful in keeping the mouth clean.

The results were excellent in all the cases depicted above. They were cleared up in an average time of four days. Neoprontosil was chosen originally because of a lack of reaction to it, as compared to sulfanilamide, in other conditions. Bargen (13) stated that in the cases of ulcerative colitis under his care, the average blood concentration of neoprontosil necessary for effective treatment was about one third of that of

sulfanilamide, sulfathiazole or sulfadiazine. In our cases, we used about two thirds of the dosage usually recommended for sulfonamide therapy.

In the above cases no other medication was given, because it was desired to prove the effectiveness of the sulfonamides in Vincent's disease. There is ample reason to include vitamins as well, e. g., ascorbic acid and nicotinic acid. The results could only be improved thereby.

Twenty cases of Vincent's Disease in children (acute infectious gingivostomatitis plus tonsillitis) were also treated. The dosage used was calculated according to the accompanying table (Table II), which was about two thirds of the average dosage recommended for the sulfonamides. Local applications prepared as noted above were also used. 90% of the cases cleared up within 72 hours. The remainder required an additional day. Here also, it is quite possible that the results could be further improved by coincident vitamin therapy.

Recently a case was seen that probably bears out our contention that Vincent's Disease is primarily an infection rather than an avitaminosis.

P. W., age 12, an inhabitant of a home for wayward girls, developed a deep, circular, punched-out ulcer about the size of a dime, at the junction of the hard and soft palates. This had existed for a week before medical attention was secured. The temperature was elevated to 101 degrees, and the white blood count was 9,000 cells, with 60% polymorphonuclear cells. A slide made from the floor of the ulcer revealed multitudes of spirilla and fusiform bacilli (Vincent's).

Six pan-vitamin capsules were given each day for four days. Each capsule contained the following constituents: 5000 U.S.P. units of Vitamin A, 500 U.S.P. units of Vitamin B1, 2 milligrams of Vitamin B2, 2 milligrams of Vitamin B6, 600 U.S.P. units of Vitamin C, 20 milligrams of Niacin Amide and 1 milligram of Pantothenic acid. At the end of four days, the ulcer had become much deeper and had increased to the size of a quarter. The patient had developed trismus and cervical gland enlargement. The temperature had risen to 102 degrees.

Because the condition of the child had deteriorated she was put on neoprontosil in adult doses (Table I). In addition, the solution was used locally every hour.

TABLE I
Classification of Acute Stomatitis

1. Acute infectious gingivostomatitis (Vincent's stomatitis)
2. Oidial stomatitis (Aphthous stomatitis or thrush)
3. Herpetic stomatitis (Recurrent ulcerative stomatitis)
4. Metallic stomatitis caused by exposure to, or treatment with lead, mercury, arsenic and gold.
5. Other forms of stomatitis occurring in agranulocytosis, primary anemia, leukemia, uremia, diabetes, sprue, scurvy, specific fevers

The patient was also given an anesthetic lozenge before each mealtime. The vitamin capsules had been discontinued. In 36 hours, the ulcer base looked fairly clean, and the ulcer itself had decreased in size. From

this point the lesion healed rapidly, and was completely healed within four days.

It was felt that in this case at least, vitamin therapy did not contribute to the successful conclusion of the condition.

TABLE 2

Table of the use of neoprontosil in patients of all ages*

Age	Dose 5 gr. tablets	Dose 24 Hours (G)
0-3 mo.	1/4 tab. every 4 hours	.5
3-6 mo.	1/2 tab. every 6 hours	.66
6-18 mo.	1/2 tab. every 4 hours	1.0
1 1/2-4 years	1 tab. every 6 hours	1.33
4-8 years	1 tab. every 4 hours	2.
8-12 years	2 tab. every 6 hours	2.66
Adult	2 tab. every 4 hours	4.

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The Significance of Enlarged Lymph Nodes*

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THE procedure of finding the significance of enlarged lymph nodes encountered in the examination of a patient constitutes one of the important chapters in physical diagnosis.

First it is necessary to differentiate certain visible or palpable swellings or lumps that may be mistaken for enlarged lymph nodes. Following are some examples of possible sources of error, such as may be observed in the examining office of a cancer clinic.

1. A mixed tumor of the parotid salivary gland may simulate an enlarged node lying behind the angle of the jaw.

2. Inflammation of the submaxillary salivary gland or of the parotid may be mistaken for an enlarged node.

3. An adenoma of the thyroid gland or the so-called lateral aberrant thyroid adenomas may simulate enlarged lymph nodes. It may be noted, however, that recently there has appeared some reason to doubt the aberrant thyroid adenomas, since they may be found to have a primary tumor in the thyroid gland, and to constitute actually a metastatic process from the thyroid to the lymph nodes of the neck.

4. Femoral, inguinal, and bladder hernias may resemble enlarged lymph nodes of the groin.

5. In women, accessory breast tissue of the tail of the

breast in the axilla may be thought to be enlarged axillary lymph nodes.

6. In women the pseudolipoma of the supraclavicular region may be mistaken for enlarged nodes.

7. von Recklinghausen's multiple neurofibromatosis may present beading along nerve trunks of neck, axillae, or inner surface of the arms, or in the groins, so as to be mistaken easily for enlarged lymph nodes. Some years ago one such case was referred as a case of suspected Hodgkin's disease. When it was observed that the supposed enlarged axillary nodes lay on the arm side of the axilla rather than on the chest wall, and that she had the characteristic cafe au lait spots of brownish pigmentation of the skin, the diagnosis of neurofibromatosis rather than Hodgkin's disease began to appear more likely, and was subsequently confirmed.

8. Occasionally exostoses of the humerus in the epitrochlear region may on hasty examination be mistaken for enlarged epitrochlear lymph nodes.

Granted that what is felt is a lymph node, it is important to be able to distinguish between a node that may be said to be actually enlarged, and one that is merely palpable. It is important to remember that lymph nodes are palpable in many normal persons, especially those who are somewhat thin. The fact that axillary, cervical, carotid, submaxillary, epitrochlear, or inguinal nodes are palpable, by no means necessarily signifies that there is anything wrong with the patient.

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Inguinal nodes, for example, in a thin person, may quite readily be felt. One has to learn to appreciate the difference between the flattened bean shape and soft consistence of a normal node, and the beginning globularity or nodularity, and usually increased consistence of an abnormal node. There is a wide borderline field here, however, with many cases in which this differentiation between normal palpable nodes and abnormal nodes is very difficult to make.

It may be stated as axiomatic that a node which is actually enlarged is a diseased node, and that it must not be ignored, but that the problem must be immediately faced, of determining the reason for its enlargement.

The various causes of enlarged lymph nodes in any site may be divided into

- (1) Inflammatory
- (2) Metabolic
- (3) Neoplastic

A convenient classification of the consistence of enlarged nodes is according to whether they may be described as hard, firm, soft, or fluctuant.

1. Inflammatory nodes may be mentioned briefly under the following headings.

- a. Bacterial inflammations. An example is tuberculosis, which may give nodes hard from calcification, or firm and resembling those of Hodgkin's disease or lymphosarcoma, or soft as in the early stages of Hodgkin's disease, lymphosarcoma or leukemia, or fluctuant by reason of caseous degeneration and liquefaction. Syphilis, typhoid, tularemia, and brucellosis are other examples of bacterial inflammatory causes of enlarged lymph nodes.

No doubt the enlargement of nodes seen with such various conditions as pediculosis capitis, abrasions of the fingers in manual workers, athlete's foot, chronic mastitis, arthritis, and some cutaneous diseases also have essentially bacterial causes. The pathologists are now beginning to diagnose dermatopathic lymph node inflammations.

- b. Fungus diseases, such as sporotrichosis, actinomycosis and coccidioidal granuloma may produce enlargement of lymph nodes.

- c. Virus diseases, such as German measles and lymphogranuloma inguinale, may be characterized by lymph node enlargement.

- d. Diseases of inflammatory nature, but of unknown etiology, such as Boeck's sarcoid (possibly a form of tuberculosis) and infectious mononucleosis, belong under the inflammatory heading

- e. One sees certain cases of slight generalized lymph node enlargement, presumably inflammatory, for which no cause is apparent, and comes to the conclusion that there may be some cases that might be designated as cases of *lymphatism*, signifying a general lymph node hyperplasia, analogous perhaps to bone marrow hyperplasia, occurring in response to some unknown etiological factor.

2. Metabolic disorders. Various lipid histiocytoses, such as Christian-Schuller's disease, may produce enlargement of lymph nodes, occasionally simulating Hodgkin's disease both clinically and histologically.

3. Neoplasms affecting lymph nodes. This is the most important of the types of processes producing enlarged nodes. Neoplasms of lymph nodes may be divided into those which are or seem to be primarily of lymph node origin, and those in which the enlargement is secondary to a malignant process beginning elsewhere.

Primary lymph node neoplasms are lymphosarcomas, lymphogenous leukemia, and Hodgkin's disease. These processes are grouped together by some writers as malignant lymphoma, a convenient generic term, but one that should, if possible, be qualified by naming the specific type of process.

1. Lymphosarcoma, as clinically seen, usually manifests itself first in some group of lymph nodes or in some aggregate of lymphatic tissue, as in the nasopharynx, tonsil, gastrointestinal wall or spleen. The most common variety is reticulum cell sarcoma. Many cases of reticulum cell sarcoma prove to be marked exceptions to what was once believed to be a rule, that lymphosarcoma is a classical example of a radiosensitive malignant tumor. Not a few cases are found which prove to be markedly radioresistant. The nodes of reticulum cell sarcoma tend to be rounded, firm and rubbery, or hard.

Special clinical varieties of reticulum cell sarcoma are worthy of mention.

Some cases present a generalized lymph node enlargement with low grade clinical activity. The borderline is difficult to draw between these cases and similar ones that prove to be essentially benign.

Some cases have a low grade relative or relative and absolute lymphocytosis, so that one is forced to say there is no sharp line between lymphosarcoma and lymphatic leukemia. It is still a question as to what extent this picture is confused by the circulation in the peripheral blood of escaped lymphosarcoma cells.

Some cases pursue an aleukemic course for years to terminate with a full blown picture of acute lymphatic leukemia.

Some cases have an acute or subacute course from onset, often with multiple cutaneous nodules, and the fever, severe anemia, and necrotic lesions of mucous membranes as in acute leukemia.

Some cases take onset with a low grade localized lymphoma, sometimes resembling an inflammatory process, with apparent easy local cure, only to generalize in a few months. The orbital lymphomas are examples of such processes for which ultimate prognosis should be very guarded.

A special variety of lymphosarcoma, known as Brill-Symmer's disease, or giant follicular hyperplasia of lymph nodes and spleen, or follicular lymphoma, was at first regarded as a benign process, remarkably radio-sensitive and curable by x-ray therapy. It is now evident that this disease is merely an initial radiosensitive stage of lymphosarcoma, and that in the later stages

becomes more aggressive, shows microscopically diffuse as well as follicular overgrowth in node biopsies, and finally becomes a more and more radioresistant reticulum cell sarcoma.

Ewing described malignant lymphocytoma as one of the varieties of lymphosarcoma, but I find this diagnosis seldom being made in the past few years. Our histological diagnoses of lymphosarcoma fall mainly into three groups,—reticulum cell sarcoma, follicular or follicular and diffuse lymphosarcoma, and a third group in which the pathologist, failing to find differentiating characters, is only able to say lymphosarcoma.

One pit-fall that has come to attention particularly in the past year has been an occasional case presenting a generalized lymph node enlargement, and a report of a biopsied lymph node as lymphosarcoma. Then it is found that the peripheral blood shows immature myeloid cells. Then we find that the sternal marrow shows a picture of myeloblastic leukemia, and upon review of the lymph node material, especially with blood stains of a smear from the node, the pathologist reports that the cells that resembled lymphocytes are myeloid cells, and that we are therefore dealing with a myeloid leukosarcoma. Some of these cases will show peculiar osteolytic and osteoplastic changes in the bones. At least two have shown on lateral x-ray views of the spine a biconcavity of the vertebral bodies.

A matter of great importance concerning lymphosarcoma is the way in which it comes to affect lymph node groups and other tissues all over the body. Is its route by ordinary metastasis, as in carcinoma, or is it a disease arising *de novo* in widely separated sites, simultaneously or at different times, as a result of some circulating causative agent? Those whose experience with lymphosarcoma is largely limited to one anatomic territory such as the head and neck, acquire the belief that lymphosarcoma has a primary focus, as in the nasopharynx, and that it metastasizes to cervical nodes by embolism, like carcinoma. In support of this belief we may cite the evidence of experience that aggressive attack upon early localized lymphosarcomas indicates that at least there is a theoretical possibility of cure of some of them. A survey of nearly 200 cases of all stages showed nearly 15 percent 5 year survivals, and about 10 percent in which there was not only 5 year survival, but apparent freedom from disease long enough to justify hope that a cure may have been accomplished.

However, considering the whole range of lymphosarcoma, one must admit that in the majority of cases the appearance of new lesions unaccountably at sites distant from the focus first observed, is much more consistent with a belief in the multicentric origin of the disease. Ewing was emphatic in insisting on the multicentric origin of lymphosarcoma. It would appear at present that for most of the cases this mode of spread prevails, and that their treatment therefore can be only palliative from the beginning, while for some cases, which at present we cannot distinguish, spread is by embolic metastases, and therefore they may offer a hope for cure, if treated aggressively early in their course. This aspect, I believe, deserves care-

ful study, in hopes that we may learn to select the cases having a chance for cure.

2. Lymphogenous leukemia, usually presents a rather uniform, symmetrical enlargement of lymph nodes and spleen and liver. The typical case of chronic lymphogenous leukemia occurs in an elderly person, and shows a marked increase in the total white cell count, with mature small lymphocytes predominating. There are all gradations from this typical picture, to the case which presents a more or less universal lymph node enlargement, but lacks any evidence of leukemia in the peripheral blood. Other atypical forms of chronic lymphogenous leukemia are numerous. Some cases present chiefly a greatly enlarged spleen, without enlargement of peripheral nodes. Others may have only the blood count of chronic lymphogenous leukemia, but no enlargement of spleen or nodes. The younger the patient, as a rule, the greater the tendency for the leukemia to be acute.

In leukemia treatment as far as we know today can be palliative only, and choice of treatment calls for wise discretion, lest the patient be made worse.

3. Lymphogranulomatosis (Hodgkin's disease).

This is a very variable process. The most common onset is simply the appearance of enlarged nodes in some peripheral group, more commonly in the neck, while the patient seemingly remains in good general health. This is the stage in which it may be of supreme importance to pay attention to the enlarged nodes, to establish a diagnosis at once, and to see that early treatment is begun promptly. The evidence indicates that early aggressive attack on localized Hodgkin's disease offers a chance for cure in some, and at least a better and longer control of the disease than if it is allowed to generalize. The attitude of some towards treatment of Hodgkin's disease, that a bare minimum sufficient to relieve symptoms is all that should be done, even in early stages, is, I believe, to be decried; and still worse is the attitude, about which a recent inquiry was received, that all treatment should be withheld in the early stage, and that one should wait until troublesome symptoms appear.

On the contrary, experience indicates that early aggressive treatment may be rewarded at least by long delay in generalization of Hodgkin's disease, and that continued close observation, and search for obscure lesions, and prompt treatment of them will greatly contribute to the length of survival and to the comfort of the patient. With respect to early aggressive treatment of localized accessible Hodgkin's disease we even advocate surgery in selected cases, to be followed by intensive x-ray therapy.

At this point I should like to mention a concept of an explanation of the bouts of fever to which, as you know, patients with Hodgkin's disease, leukemia, and lymphosarcoma are often subject. The occurrence of bouts of fever, sometimes ranging high, to 104°F. or more, has been accepted simply as one of the frequent signs of malignant lymphoma, with no particular explanation except that, given a certain amount of Hodgkin's disease, for example, the patient is likely to have fever.

We observe that sometimes the use of a sulfonamide in fairly good doses will abolish such a fever. We recall that there are many sources in the body from which bacterial invasion may occur, and that in persons with a normal lymphatic node system, protective powers are good, and the threat of invasion is constantly held off. We recall that terminally in many cases of lymphosarcoma and leukemia, definite sepsis is found. The concept of the febrile state in lymphomatous disease, then, which I should like to suggest for further attention is simply this: that in the patient with Hodgkin's disease, lymphosarcoma, or leukemia, the lymph node system is not normal, and may be incapable of handling in a normal way the invasion by bacteria and their toxins. Thus a low grade bacterial invasion first of the nodes and then of other tissues may occur or at least an unrepelled invasion by toxins may take place and I suggest that it is probably this septic or toxic state which accounts for the fever, rather than merely the activity of the lymphomatous process itself.

Secondary Enlargement of Lymph Nodes

(1) Cases of myeloblastic leukosarcoma at first passing for lymphosarcoma have already been mentioned. Myelogenous leukemia as its name signifies is primarily a disease of bone marrow. The ordinary case of chronic myelogenous leukemia does not present enlarged lymph nodes to clinical examination, although at autopsy some myeloidization of nodes is fairly commonly found on microscopic examination. It may be regarded as almost an axiom that if one can find enlarged rounded, firm lymph nodes in a case which theretofore has seemed to be one of chronic myelogenous leukemia, that case is going to have an early termination in a more nearly acute fashion than was expected.

(2) In children, especially, neurocytoma may cause localized or widespread lymph node enlargement.

(3) Metastatic carcinoma and malignant melanoma are important causes of enlargement of nodes, particularly in adults. Search for the primary focus is an important part of the duty of the first doctor who sees the patient with an enlarged node. It is important to remember that stony hardness is not necessarily a characteristic of metastatic cancer in lymph nodes. They may be quite soft, even fluctuant, if infection has been carried along with the metastasis, or if they have broken down because of the tumor's interference with blood supply, and may thus be readily mistaken for inflammatory nodes.

In nodes of the upper cervical region, metastatic carcinoma may have come from any one of several primary sites, some of which may be difficult to find. One must consider scalp and skin of face, the lips, the intraoral and intranasal mucous membranes, the nasopharynx, especially about the fossa of Rosenmüller, the hypopharynx and larynx, the nasal accessory sinuses, the Eustachian tube, the external auditory meatus, and the salivary glands.

An occasional patient may be seen presenting a hard mass in the posterior part of the submaxillary region and having at first glance no obvious primary

source of carcinoma. Further close inspection revealing a faint scar on the lower lip, inquiry then discloses that 5 or 6 years before, the patient had a V-shaped excision or treatment by radium or x-rays of a small lesion of the lip. The lesion of the lip was so small and to his mind so far in the remote past that he may neglect to mention it in his history.

In the lower cervical region and supraclavicular fossa, metastatic carcinoma may have come from any of the sites mentioned above for upper cervical nodes, and in addition one has to consider particularly various other possibilities. Among these should be mentioned the breast, esophagus, thyroid, and lung. Particular mention should be made here of the *signal node* or node of Virchow, or node of Troisier. This is usually situated in the inner part of the left supraclavicular fossa. When just beginning to be enlarged, it will almost regularly be missed by the inexperienced. To find it, it is well to let the patient's head be passively inclined somewhat forward and toward the left side, while the examiner standing in front of the sitting patient, dips the tip of his most sensitive examining finger down behind the clavicle, along its medial half, and especially between the two insertions of the sternocleidomastoid muscle. Signal nodes no more than one-half centimeter in diameter may at times thus be found, and recognized by the experienced examiner as probably significant of metastasis, because of rounded shape and usually firm to hard consistence. Formal biopsy of such a small node may be difficult, and inadvisable, because such nodes arise by transport of the tumor cells along the thoracic duct, and surgical removal of them may not only be difficult because of the small size of the node, but also somewhat hazardous because of the likelihood of damaging the thoracic duct. Yet one adept at aspiration biopsy may succeed in obtaining a diagnosis from such a node by needle puncture, with no great difficulty and with minimal risk and discomfort to the patient.

Signal nodes may occur by metastasis from any epithelial malignant tumor within the thoracic or abdominal cavity, from teratoma testis, or from any tumor that may be capable of spread by way of the thoracic duct. Occasionally, because of variation in the course of the thoracic duct, the signal node may be in the right supraclavicular region. Rarely the signal node may actually be the first signal of the existence of a malignant tumor below the level of the clavicle.

Axillary nodes. Confronted with enlarged axillary nodes, the examiner must consider the possibility of a primary site in the breast, arm, chest wall or abdominal wall, mediastinum, lung, and possibly within the abdomen. Some years ago a surgeon with considerable experience with gastric cancer asked some of the staff at Memorial how to account for gastric cancer metastasizing to left axillary nodes, without palpable enlargement of left supraclavicular nodes. He had encountered such a case, but I know of no other.

The following case illustrated the importance of an enlarged axillary node. Last year a patient came to the clinic at Memorial Hospital having been referred from a hospital in a neighboring state for recurrent ob-

struction of the small intestine. The story was that he had been operated on at the other hospital eight months previously for obstruction of the small intestine by a tumor, diagnosed by the pathologist of the other hospital as an adenocarcinoma. The slide of that tumor did not accompany the patient. Upon first examination at Memorial Hospital he presented symptoms and signs of small bowel obstruction. However, he also was found to have an enlarged firm node at the apex of the right axilla, a finding which seemed unusual in conjunction with a small bowel tumor. Inspection for a source of metastasis to the right axillary node disclosed a faint scar on the anterior surface of the right forearm. When questioned about the cause of this small scar, the patient recalled that 5 years previously a dermatologist had removed a mole from his forearm by electrocautery. This history naturally at once suggested, as a more logical explanation of his bowel tumor, that he had had a melanoma on his forearm, that it had metastasized to the axillary node of the same side, and then to the small intestine. This supposition was proved to be correct when the slide of the tumor of the small bowel was obtained, as it was melanoma, rather than adenocarcinoma.

Recently a woman from upstate New York accompanied her husband and asked for a complete physical examination for herself in order to induce him to undergo such an examination. She was aware of no symptoms, but examination disclosed, much to her surprise, an enlarged node 2 cm. in diameter in one axilla. This node was globular and hard, and therefore obviously diseased, and presumably neoplastic. Search for the primary tumor showed slight retraction of the skin of the upper outer quadrant of the breast of the same side, associated with a firm thickening of the breast tissue beneath the retracted skin. She had an advanced breast cancer.

An elderly man who had records to show that he had had chronic lymphatic leukemia for 18 years, had developed a mass of hard, enlarged nodes in his left axilla a few months before his first examination at Memorial Hospital. During the same time he had also developed a mass of enlarged hard nodes in the left groin, and a hard, fixed, sessile mass over his sacrum. On the assumption that these three hard masses were part of his lymphatic leukemic process, they were irradiated by high voltage x-rays, but showed almost no regression, despite intensive doses. Further inquiry then brought to light a scar on his left abdominal wall, and it was found that a dermatologist had removed surgically from this site a squamous carcinoma of the skin six months previously. Aspiration biopsy of the mass in the left axilla, the mass in the left groin and the tumor over the sacrum showed squamous carcinoma in all three.

When inguinal nodes are found enlarged and metastatic cancer is suspected, the external genitals, the anal margin, the skin of the lower trunk and buttocks and lower extremities, intrapelvic or intra-abdominal primary sources should be considered. Endometriosis may appear in the groin. Femoral nodes are more likely to indicate a primary source on the lower ex-

tremity.

An illustration of the importance of enlarged inguinal nodes was furnished by a case seen a few months ago. A woman only 26 years of age was referred because, although she was feeling in perfect health, a small, firm, rounded, right inguinal node had appeared. It was a single node, not over 0.5 cm. in diameter, but its globularity and firm consistence seemed significant. The referring physician stated that he had been unable to find any primary tumor, and thought that perhaps the patient had an early lymphosarcoma or Hodgkin's disease. However, during the search for a possible primary tumor, a small group of flat black moles was found about the urethral orifice. Biopsy of the inguinal node showed melanoma. Unfortunately treatment was too late in this case. The patient subsequently died of cerebral metastasis despite radical surgical dissection of vulva, groin and iliac nodes.

Recognition of beginning enlargement or retroperitoneal nodes, as in Hodgkin's disease, or lymphosarcoma, or other processes which may affect these nodes, or the recognition of their persistent residual enlargement, after they have partially regressed following radiation therapy, is something of an art, evidently requiring some practice, as they are often missed. With experience one learns to appreciate in some cases a certain fullness or resistance in the retroperitoneal region that is not normal for the particular patient who is being examined. Recalling that it has been said that often the chief function of a consultant is to do a rectal examination, it may be borne in mind that surprises in the form of small to bulky nodes may sometimes be found in the pelvic cavity.

Another point that needs stress in connection with retroperitoneal nodes is that when a laparotomy is resorted to, in order to inspect a retroperitoneal tumor, by some means or other a biopsy should be taken. It is most annoying to be presented with the problem of treating a "retroperitoneal sarcoma" when such a diagnosis is based merely on inspection and palpation of a retroperitoneal mass by a surgeon who closed the laparotomy wound without taking pains to obtain a biopsy.

To revert to the matter of rectal examination, a case in point is the following. A 50 year old Russian was referred for treatment of what was said to be lymphosarcoma. He had enlarged left supraclavicular nodes, but no enlargement of other nodes or of spleen. He had been having severe pains in his chest wall, back and lower extremities for months. Biopsy from one of the supraclavicular nodes had been diagnosed by a pathologist as lymphosarcoma, and the bone pains were explained by changes seen in many of the bones, both osteoplastic and osteolytic, regarded by our roentgenologist as consistent with lymphosarcoma. He had received considerable x-ray therapy to the painful bones without relief. However, the wide extent of bone changes and pain seemed unusual for a case of lymphosarcoma showing enlargement of only one group of nodes, and only a few months after onset of

symptoms. A rectal examination discovered a hard prostate. Then the acid phosphatase content of the blood serum was determined and was found to be several times normal. These findings were indicative of prostatic carcinoma. Then the biopsy slide of the supraclavicular node was obtained, and found to be obviously not lymphosarcoma, but a glandular carcinoma consistent with prostatic origin. Thus the rectal examination led to a discovery of the correct diagnosis.

When mediastinal nodes are enlarged, and there are no enlarged superficial nodes from which a biopsy can be taken, the diagnosis may be very difficult. Reliance on supposed characteristic roentgenographic contours, such as the scalloped lateral border of a mediastinal lymphoma, is subject to many pitfalls. One such case recently showed anaplastic epidermoid carcinoma, probably of bronchogenic origin. Another a few years ago in a man of only 28 regressed at first like Hodgkin's disease, but rapidly recurred and spread to his neck, and when the patient died, necropsy showed a grade four bronchogenic carcinoma. Seven years after removal of rectal adenoma malignum, a young woman began to cough, and was found to have an enlarged left hilar node, with extension to adjacent lung. Bronchoscopic biopsy from the left main bronchus showed adenoma malignum, identical in structure with the rectal tumor.

A young naval lieutenant on duty on a destroyer, which was on a course that caused its smoke to pass back along the deck, began to cough, as did others of the crew so exposed to smoke. When the exposure to smoke ceased the others soon stopped coughing, but he continued to cough, and soon began to expectorate a little blood. Examination showed a left hilar density and an ateleciasis of the anterior portion of the left upper lobe, with a fan-like shadow that might be consistent with bronchogenic carcinoma, Hodgkin's disease, or possibly tuberculosis. Several sputum examinations were negative for tubercle bacilli. Bronchoscopy showed nothing abnormal. Aspiration biopsy of the consolidated portion of the lung showed on section of the clot a typical structure of Hodgkin's granuloma, and the patient responded to x-ray therapy rapidly with complete disappearance of the hilar and pulmonary density, relief of symptoms and gain in weight. I know of no other instance in which a diagnosis of Hodgkin's disease has been made by aspiration biopsy of the lung. A diagnosis of Hodgkin's disease has, however, occasionally been made on a bronchoscopic biopsy. The first such instance, apparently, was reported in the New York State Journal of Medicine in 1922 by Dr. Lee M. Hurd.

Since 1927 and especially in the past few years we have accumulated a considerable series of cases presenting a rather symmetrical bilateral hilar, and tracheobronchial lymph node enlargement in patients who have not gone on to show evidence of Hodgkin's disease or lymphosarcoma elsewhere, but who on the contrary have gradually recovered and have shown, after about a year, more or less complete disappearance of the hilar enlargement. We have come to be-

lieve that most of these cases are examples of Boeck's sarcoid. This opinion is borne out by a few in which biopsy of an external node has been possible. We find that as a rule they do not show roentgenographically any of the frequently mentioned cystic changes in the bones of the hands.

Biopsy of lymph nodes. If an accessible node is enlarged the temptation is to remove it at once surgically for biopsy. However, to do so may not be to the best interests of the patient. For example, in a case presenting enlarged cervical nodes, a thorough search should be made first for a primary tumor, and if one is found, a biopsy should be taken from it, rather than to complicate the situation in the neck by a surgical biopsy. The one who is going to treat the patient will no doubt want to prove that the node is cancerous, but he can do so by needle aspiration, a procedure which should not cause any interference with prompt treatment of the neck, whether such treatment is to be by dissection or by x-rays. If a satisfactory biopsy is obtained from the primary tumor, one need not demand for a basis for therapy more histologic information about the node than to show by aspiration biopsy that it contains malignant tumor.

In the malignant lymphomas the selection of a node for biopsy requires due care. In general it is best to select if possible a node, which while accessible, is at the same time one which has been longer the seat of disease, and therefore is more likely to be representative of the process. Small satellite nodes may be more readily accessible, and removal of one of them may seem preferable for cosmetic reasons, but they may fail to establish the diagnosis. It is a common story that in the malignant lymphomas the first biopsy fails to reveal the true diagnosis. We had one case of reticulum cell sarcoma in which only the fourth biopsy during four years of observation yielded the diagnosis. Care must be taken not to crush the specimen, else the pathologist may be unable to interpret his sections. He should be furnished with adequate information about the site of the biopsy, and the clinical features of the case.

In some cases only a single fused mass of nodes is available. In such cases it is proper to take a wedge from the surface, taking pains to retract the skin so that the incision in the skin will not overlie the incision in the capsule of the tumor mass.

Aspiration biopsy should not be confused, as is so often done, with punch biopsy. The punch biopsy instrument is a cutting instrument, and actually bites a piece of tissue out. The bite may include blood vessels. Aspiration biopsy, as the name indicates, depends on aspiration of tissue into the bore of a hollow needle by means of strong negative pressure in the attached syringe. Aspiration biopsy finds use in so many situations where formal biopsy would be difficult or inadvisable that it has become indispensable.

If this sketchy survey of the possible significance of enlarged lymph nodes has done nothing more than to leave the impression with you that we all have still much to learn about them, it will have served well its purpose.

An Explanation of Appetite

By

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INTRODUCTION

THE term "appetite" in the title of this paper refers particularly to the complex state of consciousness that determines the appreciation of specific kinds and amounts of essential foods or food constituents (proteins or amino acids, fats, carbohydrates, vitamins and minerals). This might be referred to as basal, physiologically determined or inherited appetite to distinguish it from acquired or experientially conditioned appetite or appetites. Obviously an acquired appetite for certain foods is likely to be based more or less on physiologically determined or basal appetite but, if it differs from it, it would, by definition, involve the conditioning of appreciation by physiologically non-essential ingredients in the foods. Basal appetite may also be distinguished from hunger if hunger is regarded as involving only the desire to eat without discrimination while appetite is regarded as involving only the discriminative appreciation or selection of food. However, hunger (desire) and appetite (appreciation) are intimately related and can not be entirely separated from one another, although hunger may be intense while appetite is poor and vice versa. In this connection, the desire to eat which is associated with appetite is considered to be hunger whether it is mild or intense or includes prominent local (epigastric) and disagreeable sensations or more or less general and less annoying sensations. Evidence justifying these definitions, distinctions and brief explanations will become apparent in what follows.

During the past, taste has often been held to be the most important factor in appetite. I accepted this view as well as the idea that appetite would serve as a perfect guide in the selection of food after reading Horace Fletcher's *A.B.-Z. of our own Nutrition* (1) in 1908. On paying close attention to the taste of my foods then, it soon became apparent that the sugar and salt (NaCl) in these foods chiefly accounted for their appeal to my taste. Without sugar or salt ordinary foods were not appreciated. I did not consider salt to be a food at that time and therefore decided to try eating nothing but sugar until appetite or taste clearly called for something else. Thus nothing but ordinary refined (white) cane sugar was eaten during 5 days. Heartburn developed after the sugar breakfast on the second day and became the chief factor limiting the amount of sugar that could be consumed during the remainder of the 5 days. At the end of that time, sugar still seemed to be the food that appealed most to my taste but it did not satisfy, or could not be eaten in sufficient amount to satisfy, like less tasty common foods. In 1909 and 1910, heartburn was also observed

to develop after a day or two of using only honey, maple sugar and syrup or corn syrup to satisfy appetite and taste. It was also noted then that sweets become too sweet to the taste when they are no longer appreciated but that honey or maple syrup, for example, could be appreciated further after being diluted—in fact, until the amount of water that had to be added became the factor limiting the intake. The heartburn which developed with the exclusive use of sugars finally became explained, as will be seen, by a study undertaken in 1925.

My experiences with diets consisting entirely or mainly of sweets were, however, only part of an attempt to live as nearly as possible on a low protein and vegetarian regimen between 1908 and 1918 but this regimen was broken from time to time by a seemingly unexplainable or instinctive tendency to indulge periodically in the eating of meat. In order to limit the frequency of such "meat sprees" during a few years, I permitted myself the eating of meat only when it was sufficiently craved to be appreciated in the raw state and unseasoned. Raw, unseasoned beef-steak was nevertheless keenly appreciated from time to time. The tendency then was to eat or devour the raw steak rapidly and practically without tasting it. After a sufficient amount was thus ingested on two or more successive days, the impulse to swallow the meat rapidly began to lag and it always became apparent then that raw steak had a disagreeably slimy "taste" and somewhat objectionable (bloody) odor. These unpalatable characteristics of meat, in the raw or natural state, repeatedly led me to return to vegetarianism but the main point here is that neither taste nor smell seemed to explain the appreciation of raw meat (or raw eggs) after a period of protein restriction. At such times, my mouth sometimes watered copiously on becoming aware of the aroma of a steak that was being fried but no comparable watering of the mouth occurred to account for the keen periodic appreciation of raw steak or raw eggs.

After experiences like the foregoing and also experiences in fasting (as long as 26 days), I served as the subject for Dr. Carlson's study of hunger, appetite and gastric juice secretion during a 15-day fast in 1917 (2). As a result of that study, it became possible for me to recognize the periodic gastric "hunger" contractions thereafter without the need of simultaneously recording them by the balloon method. I also became familiar with making gastric aspirations on myself and noted that differences in the general feeling of well-being that occurred in 1917 were usually reflected by differences in duodenal regurgitation or in the amount of bile in the gastric contents. However, I was not satisfied that the gastric "hunger" contractions explained

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hunger. In any case, neither changes in the "hunger contractions" nor in taste seemed to explain the changes in the desire to eat which occurred with variations in the food intake. Nevertheless, I was convinced that the gastric "hunger" contractions were in some way related to hunger and that the findings of Cannon (3) and Carlson (4, 5) on this subject would have to serve as the basis of, or points of departure for, any further explanation of hunger and/or appetite. Hence, I gave the periodic fasting gastric contractions close attention after 1917 but found, in 1924, that they were experienced without the slightest desire to eat when observed at the time that the first periods of contractions occurred after a sufficiently large amount of quickly digested and rapidly absorbed food was eaten (6). This finding nevertheless still left unexplained some qualitative differences which I previously observed in hunger sensations associated with the periodic fasting gastric contractions, under differing conditions of nutrition. It seemed that variations in the fasting gastric acidity might explain these qualitative differences in gastric or epigastric hunger sensation, and a study of the subject was therefore begun in 1925. At the same time, the protein intake was varied to determine whether changes in the appreciation of protein could likewise be explained by changes in gastric acidity or by variations in some specific subjective sensation that might incidentally be revealed.

METHOD OF STUDY

In that study, a method of obtaining data concerning the acidity, volume and other characteristics of the fasting gastric contents was used which does not seem to have been used before or since, although its value should have been evident from the report in which it was first described in 1925 (7). As the primary aim was to secure data which might help to explain changes in hunger and appetite, it was imperative to minimize disturbances of natural gastric functioning. Hence, after some preliminary tests, the aspirated gastric contents were promptly returned, by tube, to the stomach after 1 cc. was separated for subsequent titration and the volume, amount of mucus or viscosity and bile contamination, if any, were noted. Thus the preceding gastric condition was restored as nearly as possible. Aspirations were generally made at half-hourly intervals. The swallowing of saliva was avoided as far as possible during intubation and the tube was removed between aspirations. Records were kept of the desire to eat, subjectively recognized gastric contractions and other pertinent sensations.

RESULTS, ERRORS AND CORRECTIONS

It soon became clear that the secretory and motor activity of the fasting stomach were interrelated (7) and that some changes in gastric sensations which were previously attributed to changes in gastric tone or motility were at least equally explainable by, or related to, changes in the volume and acidity of the gastric contents (6). The gastric acidity was found to be increased by protein restriction and decreased by protein re-alimentation or a high protein intake (8). Moreover, a peculiar periodic type of intense hunger

sensation developed when protein restriction was carried to an extreme. This hunger sensation was revealed objectively by its tendency to increase the respiratory rate (it was so intense that it took one's breath away). It disappeared with protein re-alimentation and reappeared with protein restriction and was therefore considered to be a protein-hunger sensation (9). The inverse relation which was found between the protein intake and the fasting gastric acidity and the tendency of the protein-hunger sensation to develop under extreme conditions of protein restriction seemed to be sufficient to explain the physiologic regulation of the protein intake. Similar relationships were also believed to explain the spontaneous or instinctive protein intake in rats and mice, as pylorospasm, gastric retention and peptic ulcers were found to develop as a result of protein restriction and to disappear again with protein re-alimentation (10, 11).

However, early in the study of the effect of variations in the protein intake, an error was made when the conclusion was reached that the carbohydrate intake had an effect similar to, although far lesser than, the protein intake on the fasting gastric acidity. The data upon which this erroneous conclusion was based were evidently complicated by other factors but complications were not suspected because the data supported the expected effect of the carbohydrate intake on the fasting gastric acidity. That is, it was known that carbohydrates had an effect similar to, although lesser than, proteins on the gastric digestive secretion. The protein intake was found to have the opposite effect on the gastric fasting acidity that it had on the gastric digestive acidity. Hence, it was expected that the carbohydrate intake would also have the opposite effect on the gastric fasting acidity that it had on the digestive acidity. However, recent observations showed that the carbohydrate intake or reserve has the opposite effect of the protein intake or reserve on the fasting gastric acidity (12, 13).

Another error was made in 1925 when it was concluded that short fasts increased the fasting gastric acidity like simple protein restriction. This error was due to a failure to take the fact into consideration that the pre-fasting gastric acidity was then usually lowered by a high protein intake. This error incidentally further obscured the true effect of variations in the carbohydrate intake or reserves and made it appear impossible to explain a reduction in gastric acidity during prolonged fasting excepting as a consequence of a general decrease in vital functions, as reflected by a decrease in basal metabolism. Recent observations (12, 13) nevertheless showed that short fasts decreased the gastric acidity like long fasts and also made it evident that the decrease in acidity was due to a decrease in hydration which is associated with a decrease in the carbohydrate reserves.

A third error was largely a consequence of the initial error and involved the failure to properly evaluate the effect on gastric acidity of incidental variations in the carbohydrate intake when proteins from different sources were used. As a result, differences in the effects of the different proteins did not seem explainable

on the basis of their possible effects after digestion and absorption and this led to the erroneous conclusion that the effects were due to differences in the power of the various proteins to stimulate the gastric digestive secretion and thus differentially "fatigue" the gastric secretory mechanism. However, this explanation became untenable in view of the finding of Lin and Lin (14) that the gastric secretory mechanism practically could not be fatigued. It will be seen later that the effects of differences in the incidental carbohydrate intakes largely explain the differences that were observed when proteins from different sources were used in the earlier study.

Although the recent finding that the carbohydrate intake had the opposite effect of the protein intake on the fasting gastric acidity helped to rectify the earlier errors, it also raised the question whether the effects attributed to variations in the protein intake in the earlier study could be explained by opposite effects of inverse changes in the carbohydrate intake. Inverse changes in the carbohydrate intake naturally occurred whenever the protein intake was changed while the total calorie and fat intakes were kept relatively constant. Such an explanation is nevertheless ruled out by data obtained in 1925 which show that the carbohydrate and protein intakes had similar effects on the volume of the gastric contents, instead of opposite effects such as were produced on gastric acidity. This means that the protein and carbohydrate intakes or reserves affect gastric functioning in different or specific ways and not merely in opposite ways. May not all other essential food constituents affect gastric or gastro-duodenal functioning, hunger and appetite in specific ways? This possibility is suggested when one considers the effect of variations in the food intake not only on the acidity and volume of the fasting gastric contents but also on other factors in basal gastric or gastro-duodenal functioning. The following explanations and accompanying figures should make this clear.

GENERAL EXPLANATION OF FIGURES

In figures 1 to 7, the curves show the variations in the free HCl (continuous line) and the volume (interrupted line) of the fasting gastric contents. The scale at the left applies to both acidity (clinical units of free HCl) and to volume (cc.). The dates and the time of day when the observations were made are indicated above the curves. In the first space below the curves, but only in the first 5 figures, sensations (Sens.) of gastric or gastro-duodenal origin are recorded. Somewhat vaguely felt (subjectively recognized) individual gastric "hunger" contractions are represented by short vertical lines and clearly felt gastric contractions are represented by longer vertical lines. An increase in gastric tonus or in epigastric tension is indicated by a dotted vertical line (Fig. 2—May 29) and a period of restlessness, apparently related to gastro-duodenal motor activity, is indicated by R, R, R (Fig. 2—May 30). In the space below the one in which the sensations are recorded, the presence of bile in the gastric contents is indicated. The meaning of from 1 to 3 superimposed plus signs is self-

explanatory. A plus-or-minus sign indicates the presence of only a small or diminished amount of bile. A minus sign below a plus-or-minus sign indicates a trace, further decrease or further dilution of bile and a minus sign above one or more plus signs means that the first part of the aspirate was free from bile which appeared in the later fraction.

As indicated in the figures, the observation periods generally began in the morning, shortly after the subject (the writer) rose and aspirations were usually made at half-hourly intervals until it was decided to eat or the observation periods were terminated or interrupted for other reasons. The aim was to include at least one complete period or cycle of gastric secretory and motor activity whenever practical. All of the gastric aspirations in this study were made at the home of the subject who lived alone and also purchased and prepared all of his own food. On some days (as on May 30, Fig. 2) the observation period was interrupted by a visit to the College of Medicine of the University of Illinois where blood sugar determinations (9) and blood counts (15) were made and on some other days (as on Aug. 5, Fig. 6) the gastric observation periods were not begun until after the subject returned home from the University of Chicago where psychological (16), basal metabolism (17) and other studies (9) were made. Incidentally, some observations on the development of edema were made at the Cook County Hospital (18).

EFFECT OF CHANGES IN THE PROTEIN INTAKE

In figure 1, the findings on March 20 show a pattern of basal gastric functioning such as was usually found under ordinary basal and normal nutritional conditions. The pattern on May 8 shows the effect of 17 days of protein restriction and May 9 shows the effect of a single day of protein re-alimentation (with meat) after the 17 days of protein restriction. Although the general levels of the acidity and volume of the gastric contents and the subjectively recognized gastric motor activity (number of "hunger contractions") differ considerably, the findings on each of these 3 days show the previously described (7) inverse relations between acidity and volume and between volume and motility. After 17 days of protein restriction (May 8) the acidity of the gastric contents is seen to be increased, the volume is reduced, the number of subjectively recognized "hunger contractions" is increased, gastric tonus, although not recorded, was undoubtedly also increased and bile contamination of the gastric contents or duodenal regurgitation is increased. After one day of protein re-alimentation (May 9) the gastric acidity is again somewhat reduced, the volume of the gastric contents is further reduced, the number of gastric contractions felt is increased but bile contamination of the gastric contents is reduced.

The most important effect of changes in the protein intake on basal gastric functioning still seems to be the effect on gastric acidity (8) but precisely how protein restriction increases gastric acidity and protein re-alimentation or a high protein intake reduces it remains

to be determined. As recently suggested (12) the effect of extreme variations in the protein intake can apparently be explained by the effect on the degree of hydration of the organism and the effect of moderate changes in the protein intake may be explained by opposite effects of inverse changes in the carbohydrate intake or reserves (13) but a more direct effect of changes in the protein intake on the acidity of the gastric contents also seems to be indicated. In short, a relatively direct effect of variations in the protein intake on the gastric secretion of mucus might explain the effect on gastric acidity. The importance of the gastric mucus secretion as a determiner of gastric acidity is indicated by the fact that inverse changes in the relative rates or amounts of mucus and acid secretion explain the changes in the acidity of the gastric

gastric contents. In fact, the rate of gastric secretion and duodenal regurgitation on May 8 appear to be somewhat greater than on March 20 although the average volume of the gastric contents is lower on May 8. The rate of secretion in the stomach is reflected by the rate of accumulation of the gastric contents or the slope of the curve showing the increase in volume during the periods of gastric motor quiescence. However, the rate of gastric secretion on May 9 can hardly be estimated from the curve as aspirations or determinations of the volume at shorter intervals would be needed when rapid changes take place such as occurred on this day. The rate of secretion on May 9 nevertheless was very likely somewhat lower than on May 8 and March 20. Such a decrease might be produced by an increase or prolongation of the (apparently slower) mucus se-

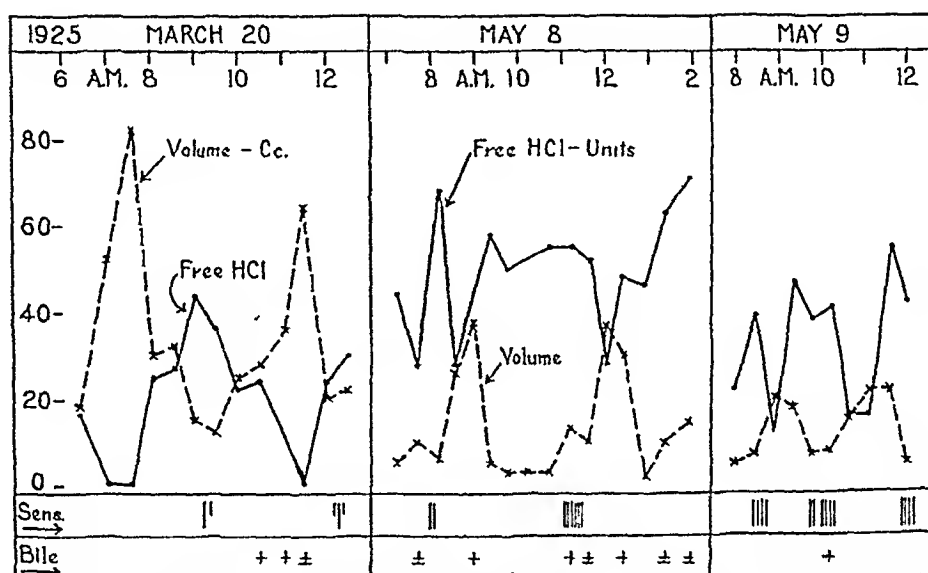


FIGURE 1. Showing the effect of changes in the protein intake on basal gastric functioning. See text for explanations.

contents which are related to the periodic changes in gastric motility and in the volume of the gastric contents (7). Similar changes in the relative rates or amounts of mucus and acid secretions may therefore also explain the changes in the average acid levels that occurred on the different days represented in figure 1. Quantitative data concerning the amount of mucus secreted were not secured as the presence of mucus was determined only by gross inspection. Detailed chemical analyses of the gastric contents would apparently be needed to obtain quantitative data as the presumably normal (glassy) type of gastric mucus is at least partly liquefied in the stomach when sufficient acid (and evidently also pepsin) is present.

The differences in the general levels of, and peaks in, the volume of the gastric contents on the 3 days represented in figure 1 are evidently mainly due to changes in gastric tonus and motility just as the chief changes in volume on separate days are related to the periodic changes in gastric tonus and motility (7). Changes in the rate of gastric secretion and duodenal regurgitation account for only minor changes in the volume of the

secretion with an inverse change (decrease) in the (relatively faster) acid secretion. This explanation is suggested by the similarities between the curve of volume on May 9, when free acid was reduced by a high protein intake, and the curve on Aug. 3 (Fig. 6), when free acid was absent because of a previous high protein intake and the secretory activity of the stomach was obviously sluggish.

The changes in tonus and motility of the fasting stomach which are indicated or implied by the findings represented in figure 1 are not easier to explain than the changes in gastric acidity. In the first place, the observation of only a few gastric "hunger" contractions on March 20 probably calls for an explanation. Whenever the balloon method of studying gastric motility was used under conditions similar to those existing on March 20, a larger number of "hunger contractions" were recorded and felt during the periods of motor activity. The presence of an inflated balloon in the stomach therefore seems to either increase the number of gastric contractions, increase their intensity or increase one's awareness of them. In fact, if the hunger

sensations which are commonly experienced with the gastric "hunger"-contractions were felt as clearly without an inflated balloon in the stomach as with one, the relationship between the sensations and the gastric contractions would have been obvious before the balloon method of study was devised. In my experiences with the balloon method of study, a few "hunger contractions" were occasionally recorded without being felt. Similar lapses may have occurred on March 20 but they are apparently common and seem explainable by a relatively high volume (10 cc. or more) of the gastric contents during the period in which sensory blackout of "hunger contractions" occur. In any case, the observations in this study indicated that gastric contractions and increases in gastric tonus are felt only after the contents of the stomach have become reduced to a level at which they no longer serve as an effective buffer between the contracting walls or can not be substantially further reduced by discharge into the duodenum. The discharge of a sufficient amount of the gastric contents into the duodenum evidently prevents the development of sufficient gastric tension to be felt just as belching reduces gastric tension. The volume of the gastric contents at the moments when gastric contractions were felt was very likely always somewhat lower than the volume observed and recorded (as in figure 1) shortly before, after or between contractions. Thus, for example, the volume of the gastric contents observed during the second "hunger period" on May 8 is likely to be misleading unless the fact is taken into consideration that the increase in volume was due to a transient duodenal (bile) regurgitation between the individual gastric contractions. The findings on May 8 incidentally show that the contents of the stomach may be reduced to less than 5cc. long before "hunger contractions" appear. This reduction in volume on May 8 was evidently due to an increase in gastric tonus (not recorded). Gastric tonus seems to be related more or less directly to gastric acidity while motility or periodicity is apparently related to other factors. The shortening of the intervals between the periods of "hunger contractions" on May 9 may have been due to a decrease in the carbohydrate intake or an inadequate fat intake when the protein intake was increased but a similar shortening of the intervals between periods of gastric contractions was also observed after one day of eating following two days of fasting. The carbohydrate intake was then obviously increased but its relation to the protein intake may have been low. Perhaps a stimulation of gastro-intestinal activity in general by any type of re-alimentation transiently shortens the intervals between the periodic fasting gastric contractions.

Bile contamination of the gastric contents or duodenal regurgitation was increased somewhat as a result of protein restriction but no evidence was found in this study that duodenal regurgitation regulates gastric acidity. Highly acid gastric contents evidently irritate the duodenum and increase regurgitation but the lowering of gastric acidity thus produced is rapidly nullified by a continued or increased acid secretion. On the other hand, an increase in the mucoid secretion in

the stomach apparently lowers gastric acidity more directly by monopolizing the available blood supply. The impression was that duodenal regurgitation might not occur at all under ideal conditions of nutrition and health. When I felt best, duodenal regurgitation did not occur, even while fasting.

The protein-hunger sensation which developed when protein restriction was carried to an extreme (9) was not identified and distinguished from the ordinary hunger sensation until after the period represented in figure 1. Some of the sensations that were attributed to "hunger contractions" on May 8 and 9 may therefore have been protein-hunger sensations. They tended to be most intense when associated with the gastric "hunger" contractions. After the protein-hunger sensation became recognized, its occurrence was specifically studied only in connection with the making of records of gastric motility by the balloon method (9). However, the protein-hunger sensations were observed from time to time, like the ordinary hunger sensations, without an inflated balloon in the stomach and the intensity of these sensations made it practically impossible to further prolong protein restriction on various occasions. Under less extreme conditions, the increase in gastric acidity (and apparently also in gastro-duodenal sensibility) which was produced by protein restriction merely seemed to increase protein-appetite—the appreciation of protein-rich foods. When a desire to eat was experienced under such circumstances and the acid contents of the fasting stomach were aspirated and again promptly returned to the stomach by tube after being neutralized with a solution of NaOH, the desire to eat was found to be completely dispelled during a period of 10 to 15 minutes and, when the desire to eat returned again after that, it was found that the gastric contents had again become acidified by the continued or an increased secretion of acid gastric juice. The effect on the desire to eat when neutralized gastric contents were returned to the stomach was like the satisfying effect of eating a steak—complete gastric or epigastric ease was produced without fullness. Evidently the neutralization of the acid in the gastric contents served to reduce gastric tonus or epigastric tension while a steak would serve a similar purpose by binding the HCl. On the other hand, when the gastric acidity was reduced by a preceding high protein intake and the protein intake after that was somewhat forced in spite of a lack of distinct appreciation, the food, at first felt like a stone in the stomach and gastric emptying was delayed. With a further forcing of the protein intake and restriction of the carbohydrate and fat intakes, gastrogenic or proteinogenic diarrhea was produced. The addition of vinegar or HCl to meat under such circumstances was found to be of value on only a few days. The addition of HCl to the aspirated fasting gastric contents before returning them to the stomach also did not clearly or uniformly increase appetite. The artificially increased gastric acidity was found to be rapidly reduced and appetite was probably not definitely increased because a heavy secretion of mucus prevented the acid from having much effect during the short time that it remained increased. Gastro-

duodenal sensibility was then evidently also low. An appetite gastric secretion (of acid) could not be provoked under such circumstances even when the mouth on such occasions watered for a preparation consisting mainly of carbohydrate and fat.

The foregoing explanations should make it clear that variations in the protein intake do not merely modify gastric acidity and hunger sensations as might have been inferred from the earlier reports (8, 9). Changes in gastric or gastro-duodenal tonus, in motility, in mucus secretion and in duodenal regurgitation are also involved. Moreover, qualitative changes in the gastric mucus and acid (?) secretions as well as in the secretion of bile, pancreatic and intestinal juices may occur and may be of more importance than the changes found in gross observations on the stomach. If each of these factors as well as the gastric (fundic or pyloric) and duodenal sensibility are more or less specifically affected by variations in the intakes or reserves of essential food factors, it seems that enough modifications in the pattern of gastro-duodenal functioning could be produced to account for all possible changes in basal appetite and to explain the natural or normal tendency to eat what is needed to restore both the general nutritional balance and the pattern of gastric functioning that is normal for the individual under satisfied condi-

tions. This view is further supported by the effect of prolonged fasting and of re-alimentation after fasting which will next be considered.

(To be continued in April 1944 Issue)

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The Cantor Sigmoidoscope

By

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INTRODUCTION

DIAGNOSIS in ano-rectal disease is usually based chiefly upon the examination. No examination may be considered complete without careful sigmoidoscopy. I prefer to combine anoscopy, proctoscopy, and sigmoidoscopy in a single examination, thus sparing the patient the successive introduction of several instruments. Even though obvious pathology is observed in the anus or rectum the examiner must never be content without complete sigmoidoscopy. Multiple pathology is not infrequent, and the discovery of bleeding hemorrhoids does not preclude a malignancy as another source of bleeding at a higher level.

In a previous paper I have reviewed the history of sigmoidoscope development (1). We will here merely recall that Howard Kelly of Baltimore introduced the first practical sigmoidoscope in 1895. His instrument was a straight tube 35 cm. long, with an obturator to facilitate introduction, and a handle for manipulation. Illumination was provided by a head mirror, and because of the length of the instrument this illumination was not entirely satisfactory.

The only important changes since that time have been in the system of illumination and in the introduction of pneumatic pressure to inflate the bowel. In the Tuttle and the Low proctoscopes illumination is by a distally placed electric lamp. All the modifications

of recent years have merely altered the position of the lamp, decreased or increased the length or the caliber of the tube, or rounded the circumference of the distal end to avoid a sharp edge. These are minor technical variations of little practical importance. Gant's sigmoidoscope (1923) offered the only radical departure in design, employing a wide-visioning telescope for bowel inspection. This instrument, however, was never developed for practical use.

My own instrument was first designed in 1940, and was developed for me by Wappler. Although I have designed blueprints for still further changes in detail, the advent of war has made it impossible to incorporate these additional features in the original instrument. I will here describe the original instrument and the one subsequent modification that priorities permitted.

Sigmoidoscopic Technique:

The technique of sigmoidoscopy is not difficult. Skill is acquired by repetition. The ability to accurately interpret the findings will develop with experience and guidance.

The position of the patient may be knee-shoulder or inverted. I prefer to invert the patient on a special table designed primarily for this examination. The scope is inserted by gentle, firm, steady pressure of the well-lubricated instrument against the sphincter muscula-

ture. When this resistance is overcome, and the instrument enters freely, the obturator is removed and further passage is under direct vision. Close examination is best performed during withdrawal of the instrument, but nothing should be overlooked during the insertion.



Figure 1. From above downward: Telescope well with inflow-outflow valves. Telescope and light unit. Obturator in sheath.

Note the condition of the lower rectal and anal mucosa. Look for pigmentary changes, petechiae, ulcerations and tumors. Observe carefully the region of the

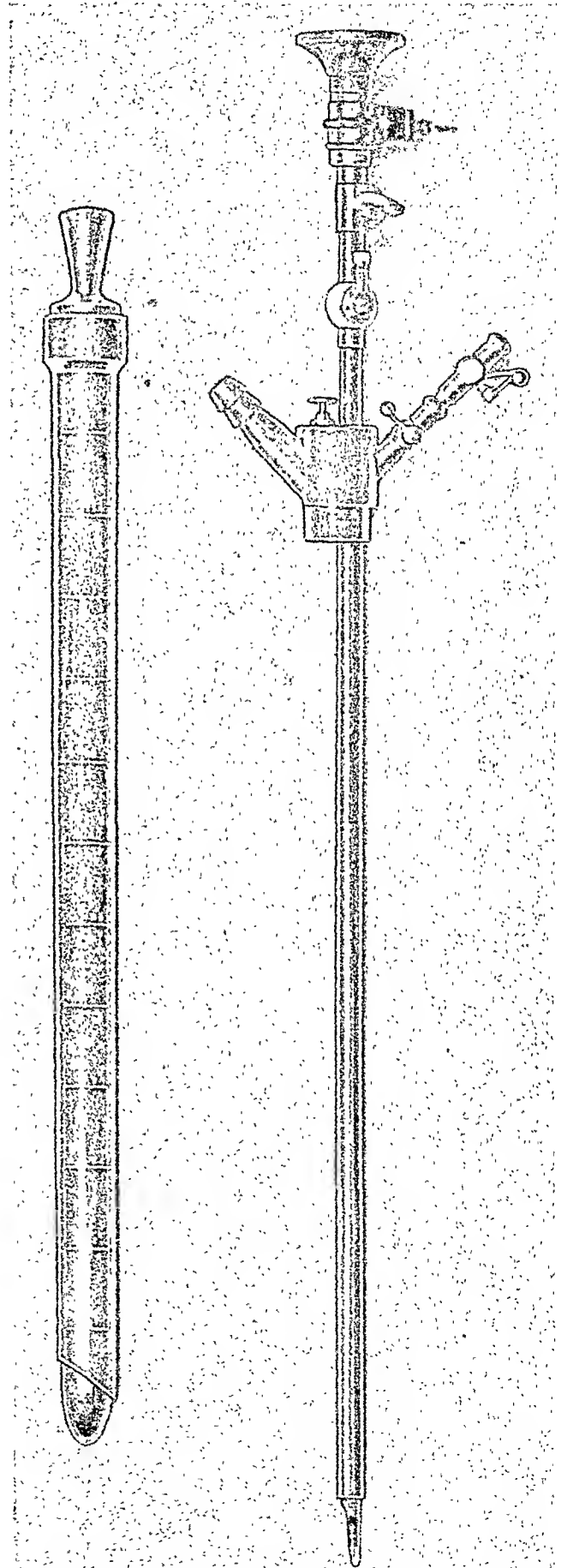


Figure 2. The telescope-irrigator assembly is shown. The obturator is in the outer sheath ready for introduction.

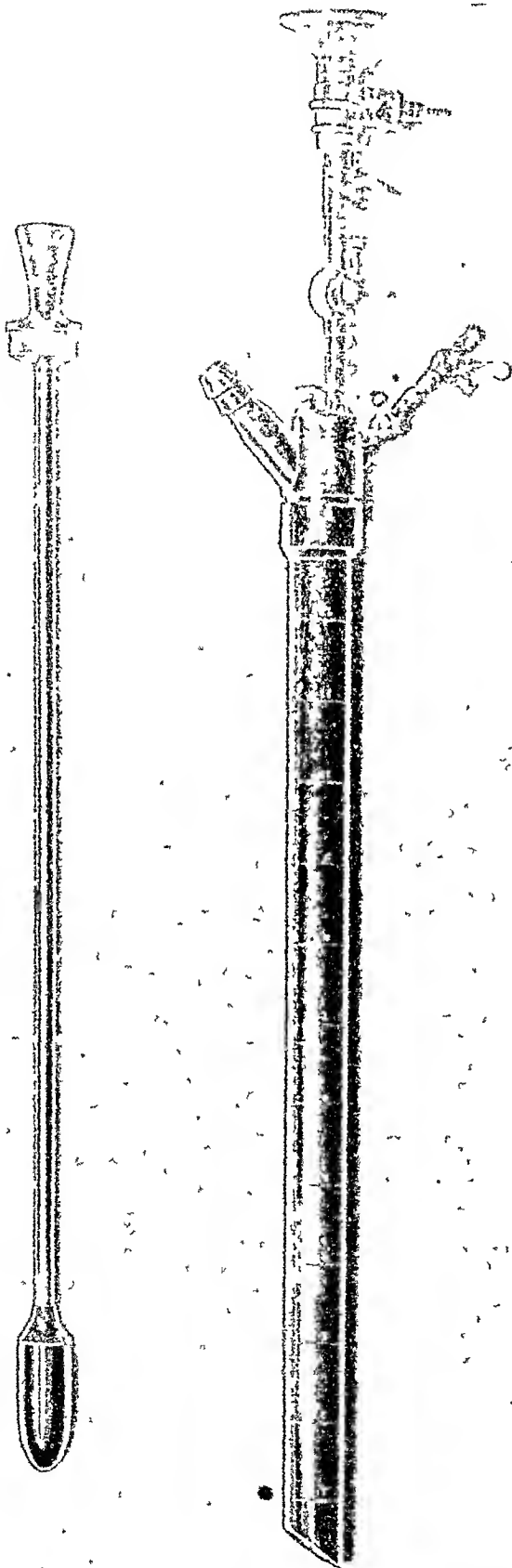


Figure 111 The obturator has been removed and the telescope-irrigator assembly has been introduced

pectinate line, the crypts for cryptitis, the papillae for hypertrophy or papillitis, and the mucosal area immediately above the pectinate line for internal hemorrhoids.

The exact direction of passage of a sigmoidoscope varies with the individual patient and the examiner's preference as to position of that patient. Some examiners prefer the left lateral position, the patient lying upon his left side, the buttocks projecting unsupported well beyond the edge of the table, the lower (left) leg straight, the upper leg fully flexed at the hip and knee. Some prefer the knee-shoulder position, the patient kneeling upon both knees, the left shoulder and left side of the face in contact with the table, the left arm being extended to the right under the patient's chest. If a tilt-table is available the inverted position is of advantage. In this position the patient is tilted head downward and is maintained in this attitude without the effort associated with holding the knee-shoulder position. The only general principles required for successful passage of a sigmoidoscope are to always pass the instrument under direct vision, always see the lumen ahead before advancing the instrument, and be gentle.

Prepare the patient beforehand by advising cleansing enemas, 6 to 8 quarts of plain tap water, both the night before and the morning of the examination. Before passing the instrument prepare the patient psychologically by informing him that at certain points it will be necessary to "straighten curves in the bowel" and that at those points there will be a cramping pain. This pain, you must assure the patient, will disappear immediately upon withdrawal of the instrument.

In general the passage takes the following course if the patient is in the inverted or the knee-shoulder position. First the instrument is moved downward and forward, toward the umbilicus for about two inches and then the obturator is removed. Next it is advanced upward (backward) and forward along the sacral curvature, over the inferior (left posterior) valve of Houston, the middle (right anterior) valve and the superior (left posterior) valve. The recto-sigmoid junction will come into view after the insertion of six to seven inches of the instrument. This will be seen as a narrowing of the lumen, and a beginning of the sigmoid rugae will be observed. At this point the average examiner experiences his first difficulty. The angulation may be so acute as to present an apparent blind ending to the rectum. No lumen may be visible in any direction. Here an experienced operator will gently manipulate first to left and then to right, seeking to open and follow the sigmoid lumen. Further passage of the instrument may lead the examiner either to the right or to the left and downward, but always under direct vision. Swab or suction the area free from any obstructing fecal matter as the examination progresses.

In certain cases a more extreme examination is required. A malignancy may be suspected at a higher level than the ten inch instrument will visualize. For such cases I have designed a new proctosigmoidoscope

The New Sigmoidoscope:

This instrument is a telescopic sigmoidoscope. I will first describe the instrument as originally devised, and then detail a recent modification that enables initial dry passage and terminal irrigation passage. The working length of the outer sheath is 32 centimeters.

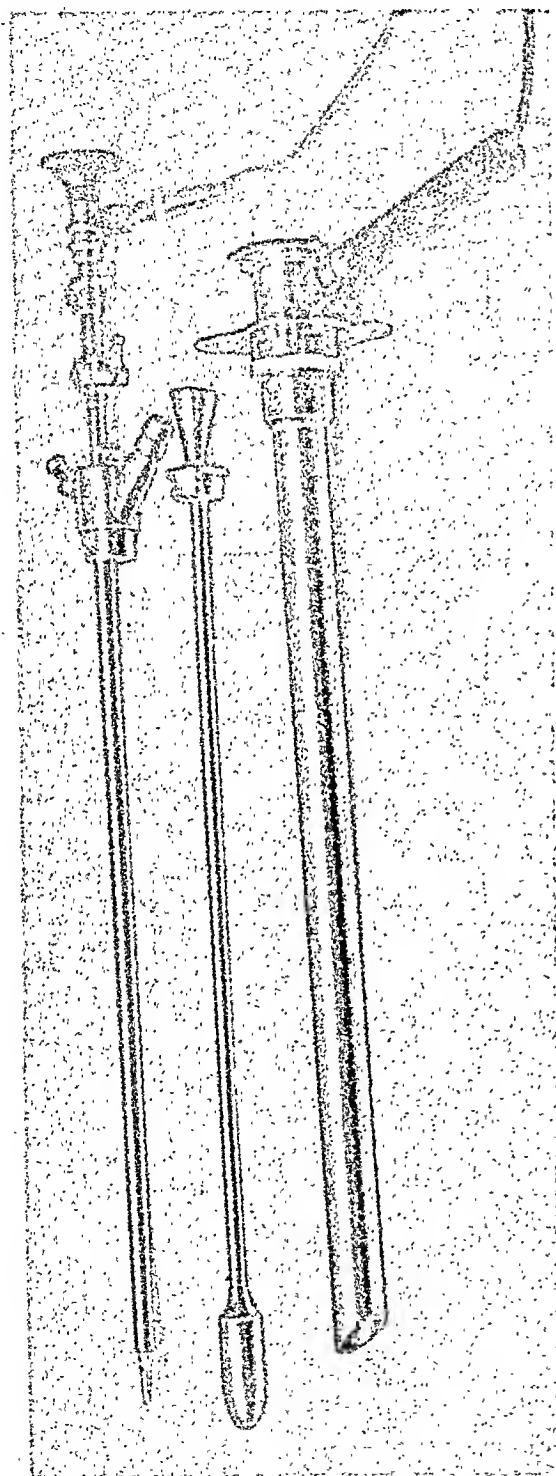


Figure IV. Telescope-irrigator assembly. Obturator. Proximal head-sheath assembly for dry initial passage.

A removable telescope of the McCarthy foroblique type enables wide-angle vision. The lamp is situated at the distal end of the telescope, and the electrical connections are an integral part of the telescope unit. A

telescope well loosely surrounds the telescope, and through this well the irrigating fluid enters the sigmoidoscope system. There is thus provided a continuous washing of the lamp and distal telescope lens.

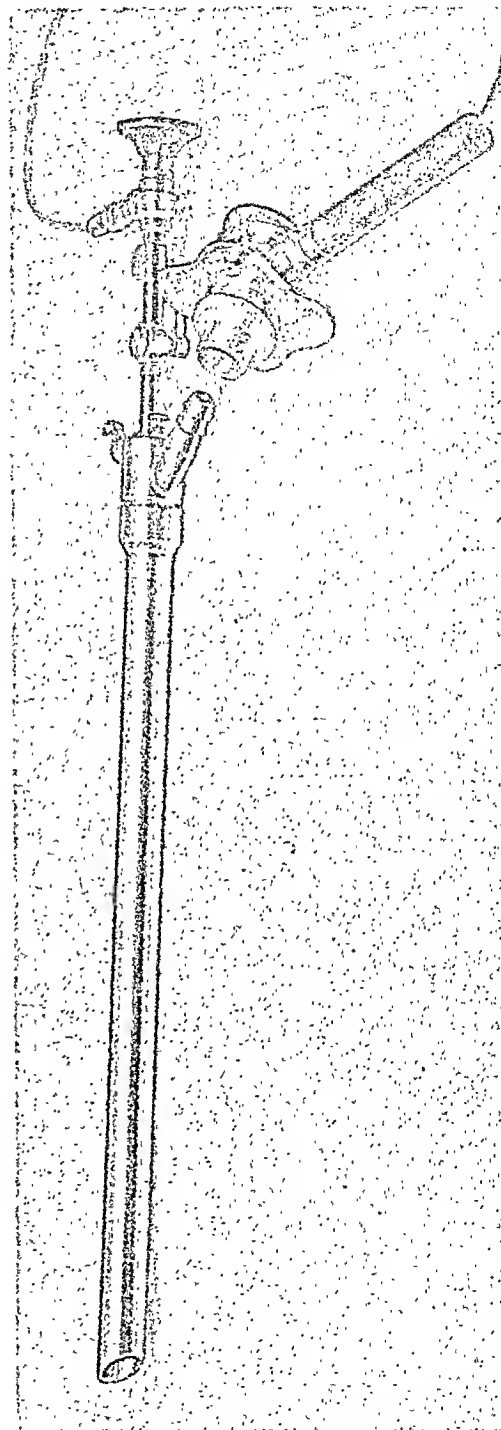


Figure V. Proximal-light head is removed after dry initial passage and telescope-irrigator assembly is introduced.

When introduced into position the telescope and well fit snugly against the interior of the upper sector of the outer sheath. A large caliber outflow tube is provided at the proximal end of the outer sheath, and thus the remaining internal area of the outer sheath is utilized for the outflow of fluid and fecal particles. A proximal sealing device provides a specimen exit and biopsy

aperture. Through this aperture a biopsy punch may be introduced to procure a specimen.

If the introduction is to be by irrigation-passage throughout the technique is as follows. The obturator is placed in the outer sheath, and the well-lubricated obturator-sheath assembly is introduced as described above. When the sphincter resistance is passed the obturator is removed and the telescope-irrigator assembly is inserted in its place. Electrical connection for the lamp, and inflow and outflow tubings are positioned for ease of examination. The actual connection of lamp cord, and inflow and outflow tubes, is made on the telescope-irrigator assembly before introducing this assembly into the outer sheath. The outflow tubing

is introduced blindly. In addition to the obturator action of the irrigating fluid, a continuous lavage of the mucosa is provided. This removes fecal obstruction that might otherwise prevent passage of the tube, and permits a more complete and accurate mucosal examination. I prefer, however, that the patient be fully prepared and cleansed by numerous self-administered enemas before examination. If the initial examination discloses incomplete preparation the telescopic assembly is immediately removed, the valve in the proximal portion of the telescope well is closed to avoid backflow, and the patient is given a thorough irrigation through the sheath-well assembly. The telescope is then re-inserted and examination may be continued.

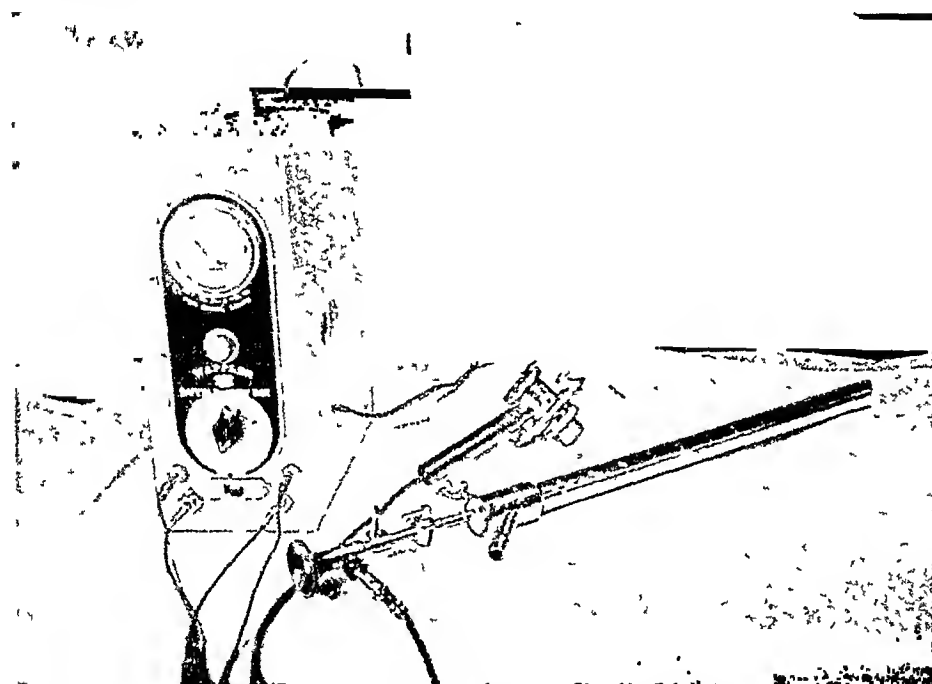


Figure VI Battery-box modified by double outlets and double-pole switch to illuminate either proximal-head lamp or telescope lamp by single throw of switch.

may run into a large bottle, a flush toilet or a special plumbing attachment. I have equipped my office with a plumbing outlet that is an integral part of a colon-irrigation apparatus. The inflow tube, leading fluid into the telescope well, may be connected with a Valentine jar or other device to permit continuous or intermittent fluid flow. I have suspended a Valentine jar from the ceiling, and provided suitable plumbing to permit ready filling of this jar with water of any desired temperature. The inflow fluid should be warm and clean.

The lamp current is now switched on and the irrigating fluid is allowed to enter until adequate visual acuity is obtained. The entire procedure of introduction and connection takes no more than one or two minutes and is extremely simple.

The further passage of the instrument must be gradual and gentle, allowing the irrigating fluid to act as a continuous obturator in separating the walls of the bowel. The irrigating fluid continuously finds and displays the lumen, and the instrument should not be in-

In some instances a continuous inflow and outflow will provide the best visual acuity, while in others a static fluid state will be more satisfactory. The mucosa presents an entirely different appearance under fluid than it does in the dry state. It appears more pinkish, more vascular, alive and plastic. The bowel wall should be carefully inspected both during the introduction and the withdrawal of the instrument. The obturator action of the fluid permits introduction to a higher level than in dry sigmoidoscopy. Indeed fluid obturation of the bowel lumen directly proximal to the instrument after its full introduction may permit inspection of a variable extent of bowel distal to the instrument tip.

If a neoplasm or other ulcerating lesion is suspected in a bowel area just beyond

the range of vision after full introduction of the instrument, the outflow fluid may be tested for occult blood. This is to be done only if the instrument passage has been very careful and there has been no trauma to the bowel wall. With the instrument introduced to its fullest extent fluid is allowed to flow into the bowel distal to that point. A sample of that fluid is obtained as it leaves the outflow tube, and that fluid is tested for occult blood. If an ulcerating neoplasm or other ulcerating lesion is present in the area of bowel flushed by the fluid, the blood washed back in that fluid will reveal the presence of that lesion.

A further use of the instrument is for therapeutic irrigations. Such irrigations may be performed under direct vision, and applied to localized areas of pathology. This, however, is not often indicated.

A modification of the above irrigation passage is to perform initial proximal insertion as a dry passage followed by distal fluid passage. This is perhaps preferred technique for the average examiner. It enables

application of ordinary sigmoidoscopic methods to the first part of the examination, and fluid-obturation passage for the more difficult distal bowel examination.

This modification was made possible by the recent development of an attachment for proximal illumina-

is then removed and the distal-lamp-irrigator assembly is introduced. The switch is thrown, extinguishing one lamp and illuminating the other, and examination progresses as above described under fluid obturation.

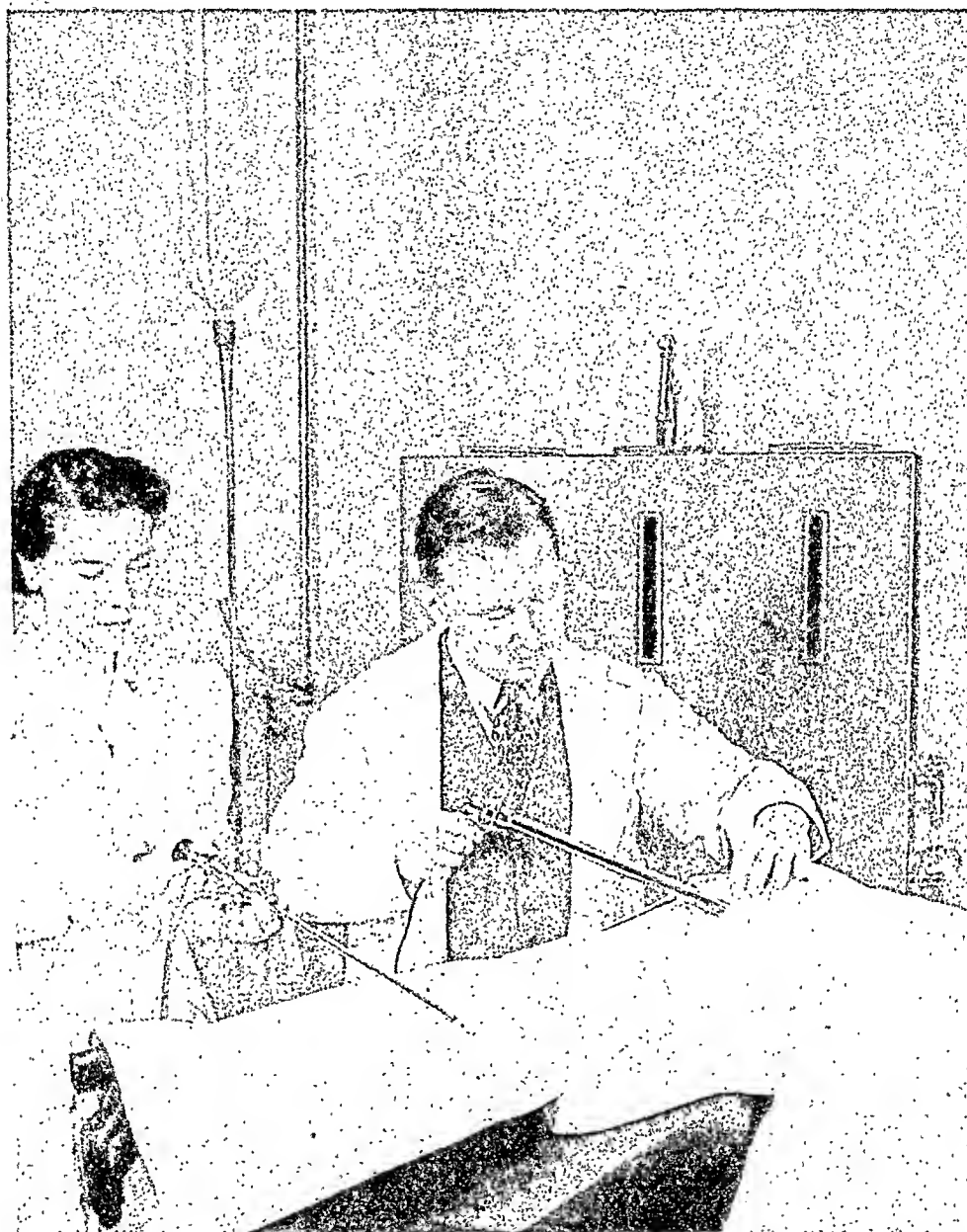


Figure VII. The instrument has been introduced, obturator removed, and the proximal-light head attached for dry passage. Nurse holds telescope-irrigator assembly. Valentine jar is suspended from ceiling. Apparatus in background is original colonic therapy device and not part of this procedure.

tion without telescopic vision and an accompanying battery box system that enables rapid switch from illumination of the proximal head to illumination of the distal lamp-irrigator assembly.

Thus the examination begins with the proximal-lighted head in position, attached to the outer 32 cm. sheath, and a dry system throughout. As in routine sigmoidoscopy the instrument is passed the usual ten inches, or less if mucosal folds or other obstruction prevents a ten inch passage. The proximal lighted head

Summary:

A new type of sigmoidoscope and new techniques of sigmoidoscopy are described. The sigmoidoscope embodies a telescope-irrigator assembly, and is so devised as to permit either proximal illumination and non-telescopic vision, or distal illumination and telescopic vision. This instrument may thus be passed with or without fluid obturation, and permits examination to a higher level than is possible with ordinary dry sigmoidoscopy.

The obturator action of the irrigating fluid facilitates high examination, and the irrigating system permits closer mucosal inspection by cleansing the bowel wall. By the introduction of a wide-angle telescopic optical

of bowel beyond the tip of the instrument after its full introduction, permitting inspection even beyond thirteen inches.

A new test for an ulcerating lesion beyond the range



Figure VIII. The telescope-irrigator assembly is now in position. The instrument is usually introduced to ten inches before this assembly is inserted to replace dry by fluid passage.

system an area larger than the circumference of the distal sheath opening may be inspected.

The under-fluid view of the bowel mucosa is more alive and more realistic than the view obtained by dry sigmoidoscopy. The fluid further acts to open an area

of vision of the instrument is described. This involves examining the return irrigating fluid from the higher area for occult blood.

I. Cantor, A. J.: A New Proctosigmoidoscope. *The Rev. of Gastroenterology*, 9:313-317 (July-Aug.), 1942.

The Early Recognition of War-Nutrition Deficiency In Children

By

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NEW YORK, N. Y.

Wartime need of protective foods. The outbreak of war caught us in the transition from the role of food for trade to the importance of food for human welfare. The change in ideas was brought about by the newer knowledge of nutrition but its applications have thus far been carried out for infants rather than for the whole family. The consumption of energy-yielding foods, i.e., bread, cereals, potatoes, sugar and fats is universal, while the utilization of the protective foods, milk, eggs, fruits and green vegetables is far from adequate. Yet the health value of a diet depends on protective foods for its power to support vigorous growth, to make blood and bones, strength of sinew and nerve. With sufficient energy-yielding food there will be no starvation but with sufficient protective food there will be no malnutrition. The gap between these two nutritional effects spells the difference between mere maintenance and optimal well-being. Federal food administration should make possible an increase in the utilization of protective foods for all American children. Morale and powers of endurance cannot be expected unless the whole population is maintained on an adequate diet. I do not mean to imply that we should cater to the nation's appetite for it is now common knowledge that Roman banquets sealed the fate of the Roman Empire and French food, the fate of France. Catering to the appetite wrecks an empire just as it does an individual. But providing protective nutrients raises the caliber of individuals,—and of these, the greatest good is possible with children. We must concentrate on national provision of protective food for every member of the family so that there will be no need for rationing of these essentials. We must fix the price in relation to the purchasing power of the poorest family and keep it at that level no matter how the value of money and the resulting cost of production may fluctuate.

Assertions have been made that family food habits are so rigid that it is almost impossible to effect a favorable change in their diet. Actually, food habits are determined not so much by the likes and dislikes but by the kind of food available. Eskimos consume enormous quantities of meat. Chinese large amounts of rice because these are plentiful. Both change their diets when other foods come within their daily reach and purchasing power. The two factors which bring about a change in diet are price and propaganda, the former is more determining amongst the poorer and the latter amongst the rich. The poorest third of the population

who are unable to buy sufficient protective foods is the weakest point of the food front. If the children of the poor are guarded against the insidious effects of dietary deficiency there need be little concern about raising the nutritional standards of rich children suffering from dietary excesses. And the number of poor children will markedly increase during the war, caught between the scissors of rising food prices and the falling family income. It remains for the government to subsidize protective foods for underprivileged children throughout the war. After all the war is a conclusive end of an epic. When it finishes, 1943 may seem as far away as 1042. Whatever the future brings, our difficulties will be lessened if we have a long range food policy which will ensure protective foods for American children, else multiple nutritional deficiency is imminent. Adults are extremely resistant to bad diets.

The chief difference between good and bad diets lies in the amount of milk, lean meat, fresh vegetables and fruits included in the daily regimen. It leads to deficiency in protein, calcium, iron and vitamins A, B₁, C, D and G. An analysis of any diets of malnourished infants or children invariably indicates not one outstanding deficiency disease but many, operating simultaneously. Physicians who thought they could maintain nutritional security by mixed diets were hopelessly in the wrong because two-thirds of the calories offered were in the form of sugar, white flour and processed fats and the remaining third could not possibly bear the necessary proteins, vitamins and minerals required for growth. Poor parents could not possibly provide their children with a balanced diet on twenty-five cents a day for the daily fare per child. A pauper's income must of necessity provide a pauper's diet, no matter how carefully it may be chosen. Even education with respect to the use of larger quantities of evaporated milk, inexpensive colored vegetables, fruits, tomatoes, legumes and nuts cannot yield optimal regimen for growing children among very low income groups in half of America's children.

Etiology of Nutritional Deficiency. The concept of deficiency disease is new. It differs from starvation in that minute rather than gross components are lacking in the daily dietary. The term has been applied primarily to results obtained from feeding experiments in animals, produced by lack of one or more vitamins and subsequently observed to occur in man. The results of animal experiments must, however, be interpreted with great caution, for there are marked species differences in nutritive requirements. For example, a lack of vitamin E in an adolescent affects primarily the reproductive system, in the rabbit it produces muscular dystrophy, and in the chick, encephalomalacia.

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Human deficiencies also differ from those of experimental animals in that the child's diet, when defective, usually lacks several nutrients. Furthermore, there are other elements besides vitamins essential for normal nutrition; hence the term deficiency disease now includes any nutrient deficiency whether it be protein, carbohydrate, fat, mineral, water or vitamin. Indeed, deficiency disease may often be an excess disease due to excessive intake of protein, carbohydrate, fat,

hausted precursory signs and symptoms reveal subclinical deficiency. Once the irreducible minimum is attained for each of the essential nutrients, manifest deficiency disease is precipitated.

1. *Inadequate nutrient reserve.* The amount of any nutrient available for use is determined by the normal body reserve of that nutrient. Some are readily stored in the body—proteins, carbohydrates, fat, vitamins A, E, F, K, minerals and the hematinic factor.

TABLE I
Etiology of Nutritional Deficiency

Deficient Reserve	Deficient Intake	Deficient Absorption	Deficient Utilization	Excessive Need
Vitamins B ₁ -C-D G-K-P Iron Iodine	Protein Vitamins B ₁ -C-D G-PP Calcium Iron Iodine	Fat-sol vitamins Ppt minerals Amino acids	Vitamins Minerals Co-action	Caloric Protein Vitamins Minerals
Prematurity Hereditary Constitution Endemic	Poverty Ignorance Food excess Food fads Anorexia Psychoses Digestive disorders Systemic disease Therapeutic diets	Digestive disorders Hypothyroidism Obstructive jaundice Celiac disease G-I allergy	Allergy Nephritis Nephrosis Poisoning Hypothyroidism	Growth Activity Infections Hyperthyroidism Leukemia

mineral, water or vitamin. Indeed, deficiency disease may often be an excess disease due to excessive intake of protein, carbohydrate or fat displacing minerals or vitamins from the diet.

Certain characteristics are applicable to indispensable nutrients in relation to the health, growth and development of children. First, they are all necessary for maintenance and growth, and even for the life of body cells. Second, they are needed only in very small amounts partaking of the nature of catalysts. Third, they cannot be synthesized by the body. Fourth, they are relatively non-toxic. Fifth, they are specific in their functional role in the body. When dietary deficiency has existed over a long period of time a deep-seated change takes place in the cell severe enough to cause functional disturbances. The marked hydration of young cells in childhood leads to prompt reactivity. If the deficiency is not corrected the altered cellular response becomes widespread and gives rise to an ever-changing variety of symptoms heralding the onset of manifest deficiency disease. Compensatory bodily adjustments conspire to conceal nutrient deficiency so long as the cellular process is still reversible. But when persistent alterations lead to structural changes in the tissues, diagnostic lesions of deficiency disease begin to appear. Body economy breaks because efficient utilization, sparing action, diminished excretion are no longer sufficient to conceal the working efficiency of catalysts at the level of the irreducible minimum for a growing organism. There is thus a wide range between daily provision of essential nutrients and minimal requirements. When this differential is being ex-

others are available in very inappreciable amounts—vitamins B₁, C, D, G, P, iron and iodine. Individual variations in body reserve of nutrients first become manifest early in infancy as a result of marked differences in prenatal dietaries; one infant may develop a deficiency disease on a limited intake of a specific nutrient while another will be protected by virtue of congenital reserves. Susceptibility to deficiency states is partly modified by hereditary tendencies, for in communities where certain deficiency diseases are endemic, many cases occur in some families while others on the same regimen escape entirely. This variation in the ability of the body to retain equivalent reserves of nutrients is probably responsible for the more frequent occurrence of certain deficiency diseases in some children and necessitates special emphasis on the minutiae in formulating a corrective nutritional regimen.

2. *Inadequate Nutrient Intake.* All essential nutrients must be offered as food or formed in the body from food since the available supply is directly proportional to the intake. Certain elements such as vitamin B₁, C, D, iron, copper and iodine are normally present in such small amounts in food that these limited nutrients may become deficient unless the diet is carefully supervised, particularly in children maintained on balanced regimens at lower levels of intake. Many conditions interfere with the proper provision of a daily dietary for the child—poverty, ignorance, food fads, anorexia, psychic disturbances, digestive derangements and systemic disease. The injurious effects are not only dependent on insufficiency of some nutrient but

also upon excesses of others; these decrease the relative intake of essential nutrients and interfere with proper balance in the diet. Dietary adequacy is dependent upon the nature of associated constituents; for example, vitamin B₁ regulates carbohydrate metabolism, which is halted at the stage of pyruvic acid in the absence of this vitamin, lack of a secondary nutrient in the diet may interfere with utilization of other nutrients; for example, absence of the intrinsic factor interferes with utilization of the extrinsic factor. Unwise choice of food results in undesirable diets and if continued over long periods of time produces deep-seated effects—in the course of months in infants; of years in children; and of a generation in adults when transmitted to the offspring. If a child's condition calls for reduction of some nutrient, the diet must contain at least a minimal amount of all necessary nutrients, otherwise deficiency disease is inevitable; for example, a child with nephritis developed protein deficiency, a child with asthma acquired beriberi having been maintained exclusively on five processed foods.

Inadequate nutrient absorption. The intestinal tract may be incapable of absorbing certain nutrients: hypothyroidism decreases absorption of minerals and may lead to iron-deficiency, anemias or to avitaminosis B₁, achylia to increased capillary permeability from avitaminosis C and P; lack of bile to defective assimilation of fats and fat-soluble vitamins; excessive intake of mineral oil to decreased absorption of vitamin A and B₁ lost in the stool. In gastrointestinal abnormalities with or without manifest symptoms some nutrients do not reach vital tissues because of failure of absorption. Hypometabolism will decrease absorption of nutrients since the level of vital activity is decreased. Psychologic factors influence the quantity and quality of foods ingested and assimilated for the motor and secretory functions of the gastrointestinal tract become greatly affected. Certain drugs may interfere with absorption of nutrients, alkali hinders intestinal permeability of iron and massive doses of iron impair absorption of phosphates. Circulatory insufficiency decreases the level of effective nutrient absorption.

Impaired nutrient utilization. Inadequate provision of nutrients does not necessarily insure their utilization at the site of need. In toxemia from chronic nephritis or infectious disease nutrients are available in the tissues without partaking in the local reactions; poisons such as lead intoxication an iron-deficiency anemia is produced uninfluenced by iron therapy because of damage to the reticulo-endothelial system, and neuritis in chemical poisoning is often due to vitamin B₁ deficiency rather than to actual chemical precipitation within the nervous tissue. In hypermetabolism, nutrients, especially iron, are properly utilized and not influenced by treatment unless co-ordinated with thyroid therapy. In allergy certain nutrients are improperly utilized if associated with others to which the body is hypersensitive.

Increased nutrient needs. Certain changes in the general condition of the child's body may increase nutrient requirements to such an extent that a diet,

previously adequate, now proves deficient. During strenuous muscular activity vitamins as well as other nutrients take part in cellular metabolism and anything that increases metabolic rate leads to increased catabolism of these substances, hence the greater nutritional requirement during muscular activity, prolonged infections, rapid growth and hypermetabolism;

TABLE 2
Daily Nutrient Requirement

	Protein gm	Ca. gm	Fe mgm	A I.U.	B ₁ mg	C mg	G mg	PP mg	D I.U.
Infancy	30	1.0	6	2000	0.5	30	0.6	5	400
Childhood	50	1.0	8	3000	0.8	50	1.2	10	600
Puberty	70	1.2	12	4000	1.2	75	1.8	15	800
Adolescence	90	1.4	15	5000	2.0	100	3.0	20	1000

for example, a child with night blindness may show rapid improvement in his powers of distinction when kept 'u bed on a diet low in vitamin A; pellagra improves spontaneously even on a pellagra-producing diet when the child is put to bed. The nutritional importance of sufficient rest and sleep is probably partly dependent upon the diminution of catabolic activity. In strenuous muscular activity more nutrients are indispensable to fulfill increased requirements. Similarly, chronic febrile diseases may give rise to deficiency because of impaired appetite and assimilation of nutrients in spite of increased metabolic rate and tissue wasting. Infection is often the exciting factor which precipitates latent symptoms of vitamin or mineral deficiency. Rapid growth requires increased intake of all nutrients as a result of higher metabolism during the spring-up periods of infancy, the period of second dentition and pubescence, hypermetabolism in fever, hyperthyroidism or leukemia, similarly increase the level of nutrient requirements and may induce deficiency disease if increased appetite does not keep pace with body needs. Finally, a diet sufficient to prevent deficiency in one locality may be unable to do so under different circumstances; for example, the diet of the negro infant may be sufficient to prevent rickets in Africa but is not sufficient in this country; an unbalanced diet may prevent occurrence of pellagra until an attack of diarrhea renders it insufficient and pellagra symptoms become manifest.

Early recognition of nutritional deficiency. Nutritional deficiencies abound in infancy and childhood in mild, latent or subclinical forms. They are multiple rather than single, ill-defined rather than specific, chronic rather than acute. Even when there are clear evidences of one deficiency, there most certainly will be signs, mild perhaps, of other deficiency states. Pure clinical pictures produced by the lack of a single vitamin rarely exist in children. The classical picture of rickets, scurvy, pellagra or beriberi is now relatively rare in this country. These end-stage deficiency disorders merely serve as pillars of orientation for the recognition of earlier manifestations of deficiency. Unfortunately, a nutritional deficiency never occurs in exactly the same manner in any two children. We must,

therefore, expect to encounter mild deficiency states in permutations and combinations approaching factorial thirty, if we assume that thirty nutrients are indispensable for health, growth and development. This means that there are several million discrete entities that challenge the clinical acumen of the physician.

Deficiency symptoms do not appear for months or years after deprivation has started, unless some acute illness precipitates the evidence within a few weeks. More often a deficiency state becomes magnified during the three periods of rapid growth, i. e., during infancy, second dentition and puberty, respectively, when nutritional needs are at their peak. The prodromal symptoms of mixed deficiency are systemic rather than local, characterized by diverse but general manifestations, especially failure to gain in weight, loss of appetite, digestive disturbances, altered disposition, nervousness, irritability and sleeplessness. Together these functional aberrations spell something in the making. Unfortunately, the two-dimensional description of this page cannot portray the three dimensional reality of

TABLE 3

Early Physical Manifestations of Nutritional Deficiency

Craniotabes—D	Fatigue—B-C-D-G-PP-Pr-Fe
Square head—D	Goiter—I
Flat occiput—D	Weight loss—A-B-C-PP
Beading ribs—D	Development delay—D
Enlarged wrists—C-D	Dentition delayed—D
Muscle weakness—D	Dental caries—Ca-P-A-C-D
Pot belly—D	Mottled enamel—F
	Nail ridges—?

the nutritional failure. It is not so much that deficiency disorders are peculiar but that the children themselves are peculiar in responding dysfunctionally to nutrient deprivation. Nature conspires to conceal the child's body weaknesses by the kind of compensatory behavior that thwarts the localization of symptoms. Yet the child's behavior should be revealing to the understanding physician. There is no need to put the child through the mill in order to arrive at a laboratory diagnosis if personal knowledge of previous diet, accurate history, physical examination and response of the child to nutritional therapy are instituted.

1.) Physical disorders.

Craniotabes. Soft spots in the skull developing between the third and eighth months of life are the first indications of vitamin D deficiency. They may occur in the region of the lamboid suture in the parietal and occipital bones which feel like parchment. Acquired soft spots must be differentiated from the congenital form due to failure of bone deposit in about 2 per cent of newborns.

Square head. Bossing of the head develops during the latter half of the first year as a result of vitamin D deficiency. There is marked bulging of the forehead and prominence of the frontal bosses. The head is flat on top and the sutures are depressed. The nati-form head of congenital lues, by contrast, appears during the early months of life.

Flat occiput. Flattening of back of the head from

pressure due to vitamin D deficiency because rickets restricts natural activity. The veins of the scalp are often prominent and the hair frequently worn in the occiput due to restlessness in sleep.

Beading ribs. Nodules at the line of the junction of the ribs and costal cartilages form the so-called rachitic rosary. It must be remembered that the costochondral junctions of normal infants during the early months are readily palpable.

Enlarged wrists. Epiphyses of the wrists and even the ankles may be sufficiently enlarged to give the joint a "double" appearance due to vitamin D deficiency. During the first few weeks of life swelling of the epiphyses may be due to congenital lues but these are painful. During the latter months of the first year of life scurvy may also cause swollen but tender epiphyses.

Pot belly. Flacid abdominal walls resulting from vitamin D deficiency offer but little resistance to enlargement of the abdomen. It is everywhere tympanic and may be as tense as a drumhead due to loss of muscle tone.

Muscle weakness. Reduced muscle tone is a striking manifestation of vitamin D deficiency, hence the delay in sitting, standing and walking in rachitic infants. The moderate resistance encountered on flexion and extension gives way to muscular weakness, fatigability and pain due to vitamin D deficiency in older children. They may have difficulty in going upstairs and complain of pain in the joints, especially in the knees and back. The condition often confused with rheumatism, should be suspected in older undernourished children.

Fatigue. Progressive decrease of the capacity for physical effort is the consequence of undernutrition. A child who lacks the subjective feeling of well-being and vigor may have a low blood sugar in his circulation and a hidden hunger for essential nutrients. These facts are not only related to the total food intake but to the frequency of meals. If a child takes a hurried breakfast insufficient for the energy needs of the mor-

TABLE 4

Early Skin Manifestations of Nutritional Deficiency

Vernix caseosa—A	Furunculosis—A
Seborrhea—B-G-P	Erythema—PP
Hyperkeratosis—A	Pallor—Pr-Fe-Cu-C
Sweating, diminished—A	Panniculus—Ca
Sweating increased—D	Turgor—H ₂ O
Whiteheads—A	Edema—Pr-C
Blackheads—A	Purpura—C-P

ing he will also miss vitamins and minerals essential for body metabolism, therefore, physical fatigue is associated with insufficient intake of calories and of vitamin B₁, C, G, D and P-P as well as of inadequate protein and iron. Lack of B₁ and P-P interfere with oxidation of dextrose.

Goiter. Visible enlargement of the thyroid is rarely great in children except in iodine deficiency, prevalent in goitrous belts. The gland is best palpated by retracting the head as far as possible, while the lower edge of the thyroid is forced up by the thumb. In this

way even slight enlargement or retrosternal placement may be demonstrated. The thyroid is uniform in enlargement, soft and compressible and may reveal bruits and thrills.

Stationary weight. Failure to gain in weight or progressive loss of weight is of great significance during the periods of active growth, i. e., during infancy, second dentition and puberty. The breast fed infant may fail to gain because of insufficient breast milk. The artificially fed infant may receive low caloric milk mixtures. The older child may be undernourished because of inadequate vitamins, proteins and minerals. Apart from low caloric intake vitamins A, B₁, C and P-P are determining factors in controlling the rate of gain in weight.

Developmental delay. Defects in nutrition especially in protein and vitamin D lead to delay in muscular development. Owing to the muscular weakness infants are delayed in holding up their heads, sitting alone, crawling, standing and walking.

Delayed dentition. Delay in the appearance of the teeth for several months due to vitamin D deficiency may occur in infants normally developed in every other way. The number of teeth very rarely remains uneven. The teeth formed often show an enamel defect in those

skin becomes dry, cool, pale, rough, wrinkled and darker than normal and often of a dull slate color.

Increased sweating. Parents complain more often of increased than of decreased sweating, hence more emphasis is placed upon this as a manifestation of vitamin D deficiency. It is especially prevalent in early infancy. The profuse secretion of acid sweat is more pronounced in the occiput and hence wets the baby's pillow.

Whiteheads and Blackheads. Facial comedones in the nasal region due to vitamin A deficiency consists of dull, red or flat or slightly comedo, discrete papules less than 0.5 cm. in diameter similar to the lesions of acne. More often they are distributed over the arterolateral aspect of the arms, upper chest and back with few on the face, abdomen and extremities. The lesions give the impression that removal of the black or white top will express pus. When such an attempt is made the cap is a thin scale which leaves a raw surface without pus.

Furunculosis. Pyogenic infections of the skin are exceedingly common in infants whose feeding is deficient in vitamin A. When the organisms gain a foothold they are very difficult to eradicate, especially over the scalp, face and shoulders.

TABLE 5
Early Manifestations of Nutritional Deficiency

Digestive

Anorexia—B₁-G-PP
Sore Gums—C
Cracked lips—G-PP
Magenta tongue—G
Sore tongue—G-PP

Flatulence—B₁-PP
Abdominal pain—B₁-D
Constipation—B₁-D
Diarrhea—C-PP
Hemorrhage—K (newborn)

Respiratory

Colds—A-C-D
Laryngospasm—Ca
Inspiratory Apnea—Ca
Dyspnea—O₂
Orthopnea—O₂

portions laid down during vitamin D deficiency.

Dental caries. Caries of deciduous and permanent teeth may be due to dietary deficiency in calcium, phosphate and vitamins A, C and D as well as to an excess of carbohydrates. Brittle teeth may develop, however, with or without caries in the presence of excess vitamin D.

Mottled enamel. Unglazed areas of enamel gradually take on a brown stain, linear or circular, as a result of excessive fluorine in drinking water.

Skin disorders.

Seborrhea. Increased activity of the sebaceous glands of the scalp, face, sternal region, axilla and pubic area may be induced by lack of vitamin B₁, G and B₆. The condition predisposes to seborrheic dermatitis, acne vulgaris and alopecia.

Hyperkeratosis. A papular eruption due to vitamin A deficiency develops first on the anterolateral surface of the arms and thighs spreading to involve the legs, abdomen, buttocks and neck. The lesions consist of dry papules up to 5 cm. in diameter arising at the site of the pilosebaceous follicles. In mild cases they are no larger than those of the ordinary goose-flesh.

Diminished sweating. Reduction in sweat as an active secretion may be due to vitamin A deficiency. The

Erythema. Rough erythematous skin lesions develop symmetrically in children maintained on diets deficient in nicotinic acid. The lesions may be absent in children not exposed to sunlight. When it becomes distinct the dermatitis is most frequently observed at the site of irritations such as the dorsum of the hand, face, neck and feet. The area is separated sharply from normal skin. Sunburn is too often the interpretation of the inexperienced examiner.

Pallor. Whiteness of the skin due to reduction of the hemoglobin in the cutaneous circulation is the consequence of protein, iron, copper or vitamin C deficiency.

Panniculus. A decrease in the fullness of the child's skin comprising adipose tissue, musculature and bound water is due to low caloric and fluid intake.

Nutritional edema. Edema of the skin and subcutaneous tissues and other parts of the body may be due to protein and vitamin C deficiency or to carbohydrate and sodium chloride excess. Frequently the condition may not be recognized by the eyes or by touch but by sudden increase in weight, especially in young infants. Even visible swelling may not always be demonstrated by pitting because of the normal elasticity of the skin. Moderate grades of edema may be recognized by pressure folds left in the skin from

wrinkles in the clothing. It is well not to confuse the pasty habitus of the lymphatic types with variable edema.

Purpura. Spontaneous hemorrhages, cutaneous or subcutaneous may be due to vitamin C or vitamin P deficiency. In the former, hemorrhages appear about the gums, eyelids, hard palate or subcutaneous tissue. In the latter, hemorrhagic spots over the abdomen or lower extremities result from vascular fragility in allergic children intolerant of the normal vitamin P content of citrus fruit.

2.) Digestive disorders.

Anorexia. Loss of appetite may be due to deficiency of vitamin B₁, G, P-P, despite the natural response for food demanded by the body in the maintenance of activity, growth and development. Indeed, the very absence of these nutrients is an aggravating factor in accelerating the development of nutritional deficiency.

Sore gums. The softening of the gums around recently erupted teeth is due to vitamin C deficiency. The gum appears swollen, congested and dark red or purple. With moderate swelling the surface becomes smooth

the consequence of inhibited tonus of the intestinal musculature.

Abdominal pain. Overdistention of the stomach and intestines and forceful peristaltic contractions may be due to deficiency in vitamin B₁ and P-P. Whatever the seat of pain its site is usually referred to the umbilicus.

Constipation. Intestinal atony may be due to deficiency in vitamins B₁ and D from early infancy. The colon becomes dilated and its content practically stagnated within the organ.

Diarrhea. Frequent passage of liquid stools may be due to deficiency in vitamin C and P-P because of progressive irritability of the small or large intestines.

Hemorrhage. Oozing of blood from the gastrointestinal tract in the newborn may be due to vitamin K deficiency. The onset is on the second or third day, the duration about three days and the cessation abrupt. Gastric hemorrhage rarely gives rise to vomiting for the bleeding is so slow that emesis is not provoked. Blood passing down the intestinal tract will color the stool black or less frequently red depending on the site

TABLE 6
Early Manifestations of Nutritional Deficiency

Sensory Manifestations	Mental Manifestations	Nervous Manifestations
Conjunctivitis—A-G-PP	Apathy—A-B ₁ -C-D-PP	Head nodding—D
Corneal injection—G	Poor memory—B ₁ -G-PP	Headache—B ₁ -G-PP-Cals
Visual fatigue—A-B ₁ -G-PP	Depression—B ₁ -G-PP-Pr	Dizziness—B ₁ -G-Fe
Dark blindness—A		Irritability—B ₁ -B ₁ -C-D-PP-Ca
Photophobia—A-G-PP		Neurasthenia—B ₁
Nystagmus—D		Muscle pain—B ₁ -C-G-PP
Touch—B ₁		Hypertonicity—B ₁ -Ca
Pain—B ₁		Sleeplessness—B ₁ -D-G-PP

and glistening and later irregular, friable and hemorrhagic.

Cracked lips. Paleness at the angles of the lips is the forerunner of angular stomatitis due to vitamin G and P-P deficiency. This is followed by piling up of a whitish tissue with pink background and superficial invasion at the site of the natural wrinkles at the corners of the mouth. Subsequently the macerated lesions become dry and a yellowish crust forms at the angles and bleeds upon removal. The lips are red, there is an increase in the transverse markings and a tendency to slight puckering, giving the appearance of a skim as on boiled milk.

Magenta tongue. Puffing, redness and magenta hue of the tongue is due to vitamin G deficiency. Changes in the epithelial capillaries and distortion of the normal papillae gradually become manifest with prolonged deficiency.

Sore tongue. If a child complains that the tongue feels enlarged and gives a burning sensation he may be lacking vitamins G and P-P. Subsequently, the tongue actually becomes swollen and red and slick in parts.

Flatulence. Recurrent accumulation of gas in the stomach and intestines may be due to lack of vitamin B₁ and P-P apart from excessive air swallowing. Expulsion of gas by way of the esophagus or bowel is

of the bleeding. If the clotting time is not too prolonged the amount of blood may be so small as to be detected only by chemical tests.

Recurrent colds. Lack of resistance may be associated with deficiency in vitamins A, C and D, hence the susceptibility to colds increasing in severity is an early indication of nutritional deficiency.

Laryngospasm. Spasm of the glottis is due to calcium deficiency. The contraction of the laryngeal muscles partially obstructs inspiration giving the characteristic crowding sounds with each expiration, especially if the child is disturbed or crying.

Dyspnea. Shortness of breath due to oxygen deficiency is a conscious desire for increased respiratory effort of pulmonary ventilation.

Orthopnea. An irresistible desire to assume a sitting position in order to obtain respiratory comfort is likewise due to oxygen deficiency.

3. Sensory disorders.

Conjunctivitis. Diffuse reddening of the conjunctiva may be due to deficiency in vitamins A, G or P-P. In vitamin A deficiency the conjunctiva are dry, tears are lessened and when the lids are held open the conjunctival tissues become drier than normal. In vitamin G deficiency there is circumcorneal injection particularly of the lower palpebral and bulbar conjunctiva.

Visual fatigue. Loss of visual acuity in dim light

may be due to deficiency in vitamins A, B₁, G and P-P. In vitamin A deficiency the child has difficulty in reading or sewing at night and stumbles in the dark because of the dim visual acuity. In other deficiencies the progress of dimness of vision is not relieved by correction of refractive errors. There is invariably the sensation of having sand or cinders in the eyes.

Photophobia. Protection of the eyes in the light is significant of vitamin A, G and P-P deficiency. In vitamin A deficiency the child is unaware of the difficulty but is manifestly blind in dim light. In other deficiencies children may bury their faces in the pillow because of intolerance to light.

Nystagmus. Irregular oscillating movements of the eyes may be manifestations of vitamin D deficiency. Unilateral nystagmus usually indicates a lesion of the brain.

Dulled sensitivity. The dimness in pain and touch sense is due to vitamin B₁ deficiency. Even the newborn responds to the prick of a pin with restlessness or crying and withdrawing of the part. The failure of anticipated response is an indication of thiamin deficiency.

4.) Nervous disorders.

Head nodding. The tendency for infants to resort to intermittent rhythmic nodding or twisting of the head is associated with vitamin D deficiency and poor illumination. There is also intermittent nystagmus and an inclination to gaze at objects out of the corners of the eye with the head slightly flexed.

Dizziness. Abnormal disturbances in the relative equilibrium of a child may be due to deficiency in vitamin B₁, G and iron if there is involvement of the vestibular branch of the 8th nerve. In Meniere's syndrome the local edema involving the vestibular apparatus develops with excess sodium intake in the diet.

TABLE 7
Infant Nutritional-Deficiency

Developmental Delay Due to Calorie Deficiency	Pseudoparalysis of Extremities Due to Vitamin C Deficiency
Infant—6 mos. failure to gain weight. Feeding—Breast, cow's milk mixture, Condensed milk, milk 15 ounces, water 15 ounces, sugar 2 T (40 cal. /lb) Symptoms—vomiting colic Signs—Schorrhea, allergic const. Rx—Evap. goat's milk, cornmeal, carrot, apple sauce—vitamin C-D	Infant—10 mos., premature Feeding—Cow's milk mixt., O.J., not tolerated, C.L.O., occasionally, cereal and vegetable, cooked Symptoms—Pallor, irritable, refused standing, fell but surgeon found no fracture Signs—Hypochromic anemia, tenderness and edema R thigh, R B C in urine

Headache. This elusive symptom may be the consequence of dietary deficiency in calories and vitamins B₁, G and P-P. Infants put their hands to their faces, pull their hair with wrinkling of the forehead and shriek with restless movements. Older children become neurasthenic as a result of nutrient deficiency rather than complain of headaches because of neuropathy.

Irritability. A child easily provoked or stimulated may be responding to deficiency in vitamins B₁, C, D, B₆, P-P and calcium rather than to nervous temperament or disease onset.

Neurasthenia. Nervous exhaustion with all its varied sensations may be due to vitamin B₁ deficiency. There are complaints of fatigability, weakness and

TABLE 8
Childhood Nutritional Deficiencies

Osteoporosis Due To Calcium Deficiency	Muscle Weakness Due To B ₁ Deficiency
Girl—4 yrs., celiac syndrome Diet—Meal, banana, apples, apricot, lettuce O.J. Symptoms—Loss weight, protruding abdomen, diarrhea, irritability, spontaneous fractures, frequent colds. Signs—Rachitis, low Ca type, osteoporosis long bones Rx—Lactic acid milk, vitamin additions	Girl—8 yrs., eczema, asthma Diet—Soy bean milk, white bread, white rice, sugar, tea, chocolate, celery, rhubarb, tapioca, olive oil, egg white. Symptoms—Pallor, restlessness, constipation, loss of weight, fatigue, calf muscle pain Signs—Tenderness calf muscles, tendon reflexes accentuated Rx—B-complex

exhaustibility, feeling of heaviness, tenseness, stiffness, numbness, tingling and other sensations. Anesthesia may be tested by squeezing the muscles of the calf.

Muscle pain. Vague pains in the lower extremities may rise from deficiency in vitamins B₁, C, G and P-P. Squatting pains due to lack of vitamin B₁ become manifest when the child is unable to rise except by h's hands. Tenderness of the legs due to vitamin C deficiency in infants leads to disapproval of handling and persistence in the recumbent position.

Hypertonicity. An infant's exaggerated responsiveness to his environment may be due to lack of vitamin B₁ and calcium. What has previously been considered a vagotonia may be due to nutrient deficiency. The infant displays excessive susceptibility to stimuli, becomes readily startled, cries continuously, shows exaggerated tendon reflexes and muscular spasms.

Sleeplessness. Disturbed sleep may be due to lack of vitamins B₁, D, G and P-P and total calories. In the first months of life crying during sleep may be an indication of nutritional disturbances. After the third month this is a premonitory sign of vitamin D deficiency. Even in infants sleeplessness may be an expression of neuropathy aggravated by vitamin B₁ deficiency. In older children fretfulness and restlessness during sleep may indicate vitamin P-P deficiency.

Management of nutritional deficiency. The object of nutritional therapy is to restore the child to well-being. There is such a wide gap between the amount of essential nutrients needed to prevent deficiency and that needed to insure optimal health and growth that the assessment of the individual child must be made with a view towards improving his nutritional status and preventing deficiency recurrences. Whether the manifestations arose from a lack of water-soluble or a fat-soluble vitamin, a multiple deficiency is invariably present even though symptoms are not appar-

is any evidence of dehydration the fluid requirement must be promptly fulfilled by parenteral administration and in the absence of abdominal distention, 5 per cent dextrose solution or 0.9 per cent saline solution may be given intraperitoneally at six-hour intervals. Parenteral administration of fluid does not of course preclude adequate provision by mouth, unless the condition is associated with vomiting.

The milk mixture is best prepared from acid, evaporated or dried milk, reinforced with corn syrup or maltose dextrin. Whole lactic-acid milk, eleven parts and Karo syrup one part, yields a caloric value of 30 calories to the ounce. In the presence of digestive disturbance a small amount of feeding is offered initially to determine the infant's digestive capacity. At the beginning, one-half ounce of the formula is given at three-hour intervals throughout the twenty-four hour period. Then the feedings may be gradually increased by 1 or 2 drams according to tolerance. The initial milk mixture should provide about 25 calories per pound of actual body weight in 24 hours and the final feeding about 50 calories per pound of expected body weight. This may be brought about rapidly for infants with good digestive capacities and more slowly for those with limited capacities.

Concentrated cow's milk mixtures consist of the following: (1) Acid milk, preferably skimmed or whole lactic-acid milk, with added Karo syrup or maltose dextrin; (2) Protein milk with added carbohydrate; (3) Butter-flour mixture; (4) Olac, mixed in the proportion of one ounce of powder to four ounces of water and maltose dextrin added; (5) Skimmed milk with 15 per cent added maltose dextrin, corn syrup or cane sugar. Successful high-caloric feedings contain such a concentration of carbohydrate that they can only be given for several weeks and discontinued when there are indications of protein deficiency. One of the earliest manifestations is pasty appearance, hydrous skin, nutritional edema resulting in abnormal rates of gain in weight, or sudden losses in weight, due to elimination of stored water. Unbalanced mixtures are contraindicated during hot weather, especially if dystrophy is associated with diarrhea. In such instances a more balanced lactic-acid milk formula containing less carbohydrate should displace the more concentrated feeding.

Cow's milk mixture alone cannot fulfill all nutritional requirements of the dystrophic infant any more than of the normal infant. When a suitable formula has been adapted to the infants' digestive capacity and gradually concentrated so that he receives as much as 100 calories per pound of actual weight, other essential nutrients may be gradually introduced. Vitamin supplements are given first consideration; concentrated sources of vitamins A and D are preferable to oil because it is not well borne; brewer's yeast powder may be added to the formula to provide additional B₁, G and others of the complex. Raw strained fruit juices should be added in increasing amounts to provide vitamin C and if these are contraindicated ascorbic-acid tablets may be offered. Solid foods are gradually introduced to provide the total food intake of

a normal infant of his age; thoroughly cooked, refined cereals are added in small amounts and if they are well borne the alkaline-forming Pabulum may be offered. Vegetable puree, strained fruit, potato, rice, banana, scraped beef are introduced gradually to other feedings according to tolerance.

The older child with malnutrition requires two to three times the amount of food of the normal child of similar age to make satisfactory gains in weight. It may be provided by adding mid-morning and mid-

TABLE 11
Superior Sources of Protective Nutrients

Calcium	A	B ₁	G
Cheese	Fish oils	Pork	Liver
Milk	Liver	Beans	Viscera
Turnip top	Egg yolk	Wheat germ	Meat
Almonds	Butter	Oatmeal	Milk
Kale	Greens	Peanuts	Egg yolk
Watercress	Cantaloupe	Brown rice	Cheese
Figs	Peaches	Yeast	Peanuts
			Greens

Iron	D	C	PP
Liver	Fish oils	Citrus fruits	Liver
Oysters	Egg yolk	Greens	Pork
Meat	Yeast, irradi.	Berries	Viscera
Egg yolk	Caviar	Liver	Peanuts
Beans		Brains	Beets
Greens		Parsley	Yeast
Apricots		Currants	
Peaches		Peppers	
Whole wheat			

afternoon feedings to the usual three meal-a-day regimen, particularly when the appetite is good and the energy excessive. The child may, however, be maintained on a balanced diet distributed in three meals, additional food being gradually increased according to digestive capacity. The dietary prescribed should be a modification of that ordinarily used at home rather than a completely new regimen. If the child's previous diet is evaluated for excesses or deficiencies it may be re-adjusted by suitable additions or eliminations. The diet is seldom faulty with respect to one factor alone, for excess of one substance and deficiency of another is the common error. Nutritional failure may be halted by according equal importance to all nutrients. A healthy desire for food may be instilled by diminishing the sugar and fat content and only water or fruit juice offered between meals. At first a three-meal regimen is instituted without bribing, coaxing or forcing food. Breakfast should consist of stewed fruit, fresh or dried; coarse cereals such as oatmeal or cornmeal; bacon or fish; skimmed milk and whole-wheat bread with a scanty amount of butter. Dinner should consist of vegetables, raw and cooked; visceral meats or fish; stewed fruit, raw or dried; and skimmed milk. Supper should consist of vegetables, raw or cooked; skimmed milk; stewed fruit or milk pudding. Indigestible articles of food should not be given to tempt the appetite and cod liver oil, malts

of these nerve changes being secondary and associated with increased pressure on brain and nerve cells. They believe, however, that instead of bone overgrowth, there is a prompt retardation of bone growth in vitamin A deficiency, while the nervous and perhaps other soft tissues continue to grow until retarded by inanition. This disproportionate growth results in pressure on those parts of the nervous system surrounded by bone, and leads to mechanical damage and irregular nerve degeneration. Both lines of attack on this problem should be studied by reference to the original papers (J. Physiol. 91, 380, 1938). The exact role of vitamin A deficiency in bone growth remains an obviously fundamental problem for further investigation.

Vitamin distribution in wheat flour. It is now fairly well established that the niacin content of wheat germ is actually less than that of the whole wheat berry. Only in the case of riboflavin does the wheat germ appear to maintain its original reputation. The wheat germ is about six times as rich in riboflavin as the whole wheat. An increase in the extraction of flour from 60 to 75 per cent more than trebled the percent of total thiamine, while riboflavin and niacin increased by not more than 50 per cent. This indicates that the nutritional benefits obtained by increased extraction were largely due to increased thiamine content. If extraction is increased to 85 per cent, the increase in per cent of total thiamine is about nine fold, while the increase in riboflavin and niacin are only about one third as much. It was concluded that pantothenic acid and biotin exist in patent flour in quantities approximately one-half that found in whole wheat. Concentrations of these vitamins are highest in bran, and bran must be added to get appreciable increases of these vitamins from increased extraction. (Food Industries, 15, 78, 1943). It appears that nongerm tissues, surrounding the germ, contribute considerably to the vitamin potency of wheat and high extraction flours, and current emphasis on the wheat germ should not overshadow this fact.

Prevalence of rickets in children. Apparently there is more subclinical rickets in America than had been supposed. (Am. J. Dis. Child. 66, 1, 1943). By a histological examination of the middle ribs (especially the anterior costochondral junctions of the ribs) of children dying of various diseases other than rickets, it was found that of 230 children examined post-mortem, 107 were found to present some evidence of rickets,—slight in 53, moderate in 43, and advanced in 11 cases. The highest incidence was in the third year of life. Roentgenological examination of the cadavers revealed X-ray evidence in only 6 out of the 107 cases, and none of these was in the age group 5 to 14 years. It was felt that the diseases from which the children died had nothing to do with the presence of rickets. The investigation shows the importance of guarding against rickets in sick children, and also emphasizes the need of continuing the administration

of vitamin D throughout the period of skeletal growth.

The effect of diet on toxic agents. (Nutrition Reviews, 1, 88, 168, 247, 274, 1943). A diet high in carbohydrate and protein and low in fat seems to protect rats from the effects of trinitrotoluene poisoning, and presumably these facts may be applied to man. The nature of the diet eaten by persons exposed to the risks of trinitrotoluene poisoning may have something to do with their susceptibility to liver damage (New Orleans Med. & Surg. J., 95, 511, 1943). Treatment of trinitrotoluene poisoning has included a high carbohydrate, low-fat diet with additional vitamin B-complex and vitamin C and additional protein, but the same regimen has not, as yet, been used as a possible preventive measure.

Temperature effect upon vitamin requirements. It was found that optimal thiamin requirement for rats was twice as high at 91 degrees F as at 65 degrees F, and that rat requirements for optimal growth are twice as high at 91 degrees F as at 68 degrees F for thiamin and pyridoxine, and over five times as high for choline. (Am. J. Physiol., 133, 525, 1941) (Arch. Biochem. 1, 73, 1942). Now it appears that riboflavin and pyridoxine requirements for optimal growth of young rats seem to be the same in both heat and cold. Of all B-actons, only thiamin and choline exhibit heightened requirements in tropical heat. However, on careful examination of the experiments on which these conclusions were based (Arch. Biochem. 2, 159, 1943), it is found that the vitamins were incorporated in the diets and not fed separately, as a result of which confusion results, because of the effects of heat in depressing the appetite and the total amounts of food eaten. Further work is needed to determine the effects of temperature on vitamin requirements.

Urinary pigments in niacin deficiency. There was rejoicing when it was stated that persons with pellagra excreted in the urine certain porphyrins which could be detected by simple laboratory methods, for this promised a good clinical means of diagnosing thiamin deficiency, especially when it was stated that the porphyrins disappeared after the administration of niacin. (Quart. J. Med., 6, 305, 1937). But it was soon found that the reaction given by the test was due to uroporosein and not to porphyrins at all. (Proc. Soc. Exp. Biol. Med., 41, 591, 1939). Even the uroporosein cannot be used as a dependable guide to niacin deficiency because it lacks specificity (Ann. Int. Med., 19, 183, 1943). The chief variable upon which the spontaneous uroporosein test depends is an oxidizing agent in the urine, whose nature is still undetermined. The uroporosein reaction is negative in the urine of dogs with black tongue (Ann. Int. Med., 19, 200, 1943).

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tal and physical tensions, eventually acquire organic changes as a result, but his relation to his environment may be rendered dangerous. This latter appears in persons who, as Dunbar shows, are "subject" to serial bone fractures.

The book is primarily a record of research studies on patients suffering from the following conditions—cardiovascular disease, diabetes, fracture, gastrointestinal disease and allergy. The psychic components in the individual case are first located through the taking of a "psychosomatic history." It became necessary to get an answer to the question as to whether certain types of physical disease carried psychiatric or mental conditions somewhat characteristic of the clinical group. It is of vast interest that the studies suggest this to be the case. Over a period of five years, and in some cases much longer, more than 100 cases at the Presbyterian Hospital were subjected to observations in both physiological and psychological terms. In some instances it was found that the Rorschach tests were of definite value in detecting tendencies that had been missed in the psychological examination. The *focus* of the psychosomatic history concerns the relationship of character to physical constitution. The scope of the history, which requires a social record as well, deals with patterns of behavior and responses to difficulties, spheres of adjustment and injuries from the environment, defenses and reactions to stress, and an evaluation of these elements in terms of factors predisposing to illness. The history is obtained from spontaneous statements of the patient, and evaluation of his attitude and inconsistencies. Many patients need symptoms for the satisfaction of their psychological condition, and once a single manifestation of spasm, for example, is taken care of, a new focus springs up elsewhere. Dream analysis is also used. Then one must make an evaluation of the patient's psychosomatic reaction pattern, which in a word, is how he reacts mentally and physically to stimuli from the environment and from his own ideas and concepts and emotions. Observation of the patient's shifting tensions gives important clues to what he may be repressing. The relationship between emotional material and the incidence of attacks of symptoms or pain is also to be determined. A personal interest in the patient, which to be effective must be unfeigned, is essential for getting the maximum degree of cooperation. Free association was frequently employed. Occasionally the revised Stanford-Binet test was used. In each of the groups of patients studied, it was possible to summarize the findings under a group of headings, the summary being called "the profile." The profile included conclusions as respects *family history, personal data* (relatives, etc.), *injuries, general adjustment* (education, work record, income and vocational level, social relationships, sexual adjustment, attitude to family), *characteristic behavior pattern, neurotic traits, addictions and interests, life situation, immediately prior to illness or injury, reaction to the illness, area of focal conflict and characteristic reaction*. It was found, for example, that fracture cases showed

a remarkable freedom from illness as compared with the population as a whole, but they showed a high record of previous accidents, a high percentage of childless marriages, and small families. Some of them show marked opposition to authority, a complex which was variously solved. The group with hypertensive cardiovascular disease show an extremely high illness record, a high marriage rate and large families, are predominantly introverted, tend to have neurotic tendencies of an impulsive type, marked perfectionist tendencies and obsessive doubts, explosive expression of feelings, a habit of relieving tensions through dissipation, and they usually are surcharged with energy for which no adequate outlet can be found. Persons with coronary occlusion are extratensive, and have a "distinguished look" and their typical asceticism and hard work cloaks and rationalizes many compulsions. They seldom allow themselves freedom in emotional expression and are quick to form judgments. "The coronary accident is precipitated by an apparently irreparable mutilation of their picture of themselves through external threats to their authoritative rule." Similar characterizations are set forth for other disease groups,—anginal syndrome, rheumatic disease and rheumatoid arthritis, diabetes. These are extremely interesting and stimulating. The reader will realize that what Dr. Dunbar and her associates are doing on a large scale and with scientific care, is more or less what he has always been doing in an informal, less effective way,—he has been quietly forming opinions about the personalities of his patients. The question respecting the value of psychosomatic treatment is readily answered. This may be expected to have good results if applied early. In private practice one is limited by time factors and by the usual lack of familiarity with technical psychological problems. As research progresses in this fascinating field, the results will accrue to the education of the general man and internist. Everyone in medicine ought to read this book, for it marks the first real charting of a new method of studying patients, and, so far as it has gone, becomes the chief argument, on its own internal evidence, for the probable validity of the idea of mental and physical identity. Incidentally, Hoeber has made another excellent production which leaves nothing to be desired by the fussiest of students of format.

The Modern Management of Colitis. By J. Arnold Borgen, M.D. 332 pp. 148 figs. Charles C. Thomas, Springfield, Illinois, 1943. Price: \$7.00.

This is an excellent book containing as it does detailed descriptions of all the nine different types of chronic ulcerative colitis together with a chapter on the irritable bowel and another on conditions which may be confused with colitis. The book is beautifully illustrated and well documented, and the text is interesting. There is much on treatment and much valuable material on the handling of the many miserable complications which often come to plague these patients.

No one who deals with these cases can afford to be without this book which embodies Dr. Borgen's enormous experience in the field.

The case is presented of an endometriosis which was treated by radium but complication due to reactions to treatment developed. These complications were brought under control by drainage of a pelvic abscess and by colostomy.—D. A. Woecker.

FELSEN, J.: *Intestinal vascular sclerosis*. (*The Hebrew Med. J.*, 2, 189/, 1942.)

"Intestinal vascular sclerosis is a condition of the mesenteric blood vessels usually associated with old age and after accompanied by disordered bowel function. . . . The end result is a narrow rigid vessel which is unresponsive to the ever-changing circulatory requirements of the organs supplied. . . . In the mild, moderate, or recanalized forms of vascular sclerosis few or no symptoms may be present." The chief clinical signs and symptoms in more advanced stages are abdominal distension, constipation, indigestion and abdominal cramps. The condition is most common in the sixth decade and later. Felsen thinks that intestinal vascular sclerosis is only a topical manifestation of a more generalized condition of the vascular system. The relative ischemia and anoxemia in intestinal vascular sclerosis is believed to be responsible for the symptomatology. Therapy is based on considerations of the pathologic physiology existing. Supportive measures when a cardiac condition is co-existent are recommended. Dietary limitations, intestinal aspiration and intestinal oxygenation are beneficial in relieving symptoms.—G. Klenner.

KILROY, EDWARD J.: *Diverticulosis and diverticulitis of the colon*. (*California and West. Med.*, V. 58, P. 341, 1943.)

This is a common condition existing in 5 to 15 per cent of the population. About 5 to 10 per cent of the cases develop complications and of these 12 to 20 per cent require surgical intervention. These diverticulae do not exist at birth, occur in the fourth, fifth, sixth and seventh decades of life and are produced by obesity, constipation, flatulency, weakness in the longitudinal muscle fibres of the colon. After the diverticulae once develop, there is no way of eliminating them.—Courtesy Biological Abstract.

LIVER AND GALLBLADDER

SHAPIRO, S., REDISH, M. H., AND CAMPBELL, H. A.: *Prothrombin: variable effect of anticoagulants in liver disease*. (*Am. J. Med. Sci.*, V. 205, P. 808, June 1943.)

Plasma prothrombin time is suggested as being an index of the ability of the liver to elaborate prothrombin. Prolongation of the pre-existing plasma prothrombin time in cirrhosis may be indicative of failure of this liver function. The minimal dose of Dicumoral necessary to prolong prothrombin time in normal individuals was 100 milligrams; in liver cirrhosis less than half of this dose was found effective in prolonging prothrombin time.—G. Klenner.

MEYER, K. A., STEIGMANN, F., POPPER, H. AND WALTERS, W. H.: *Influence of vitamin A metabolism on liver damage*. (*Arch. Surg.*, V. 47, P. 26, July 1943.)

Vitamin A levels in the blood and Vitamin A content of the liver were studied before and after feeding large doses of the vitamin. In conditions of liver damage the level of vitamin A in the plasma is low. In the absence of demonstrable nutritional deficiency, a low plasma level of vitamin A is indicative of functional deficiency. Presumably the liver cannot release vitamin A from its stores and also there exists faulty absorption of vitamin A from the intestine. It is believed that large doses of vitamin A are needed in hepatic cases in order to compensate for the decreased intestinal absorption.—G. Klenner.

DIBLE, J. H., McMILLAN, J. AND SHERLOCK, S.P. V.: *Pathology—acute hepatitis: aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice*. (*Lancet*, 245: P. 402, Oct. 2, 1943.)

Liver biopsy studies by the aspiration method of Iversen and Roholm were made on 56 patients. The usual risk by hemorrhage is about one per cent mortality, but the authors found this risk to be such in only severe cases with jaundice. A total of 126 transpleural punctures were made. Two patients with advanced disease or acute necrosis of the liver died after 48 hours. The histologic sections were classified as to the extent of hepatic involvement, such as zonal, diffuse, or mixed diffuse and zonal. Also noted was residual fibrosis when seen in the healing stages. The histologic changes are described. The authors feel that the puncture aspirations are representative of the entire liver. They conclude their studies with evidence that epidemic jaundice is a hepatitis and not a duodeno-biliary catarrh. It is suggested that the damaged liver cells may accumulate bile because they are unable to excrete it. In 12 of 56 cases, 50 per cent of the hepatic cells showed histologic damage, but the normal course was to complete recovery. It is agreed that sub-acute or acute necrosis and cirrhosis could follow epidemic hepatitis. No histological criteria could be determined to differentiate the lesions from epidemic hepatitis, arsenotherapy, or serum inoculations.—William D. Beamer.

THERAPEUTICS

ANGLEM, T. J. AND CLUTE, H. M.: *Intraperitoneal use of sulfonamide in gastrointestinal resections*. (*New England J. Med.*, V. 229, P. 423, Sept. 1943.)

From their experience with the local intraperitoneal use of sulfonamides in 75 cases of digestive tract surgery, the authors are convinced that the procedure is extremely valuable. The sulfonamide was applied along the suture line of the operated viscus in doses not to exceed 8 grams. No peritonitis deaths were present; the only death among the 75 patients was not due to intraperitoneal infection. A toxic reaction, in the nature of hepatitis, was seen in only one case and was not fatal.—G. Klenner.

WOLF, S.: *Relation of gastric function to nausea in man.* (*J. Clin. Invest.*, V. 22, P. 877, Nov. 1943.)

Studies were made on 2 normal subjects and on one with a large gastric fistula. While supine, a recording of pressure changes was made by means of an inflated intragastric balloon. Sweating on the forehead was noted by resistance changes recorded by the Wheatstone bridge. Color and pulse rate were also noted. Nausea was induced by caloric vestibular stimulation, swinging or rotation, or fear and withdrawal. In all, twenty-five studies were made. A decrease of gastric motility occurred within one minute after stimulation, and antedated nausea. The other objective symptoms, pallor, sweating, salivation etc. occurred in two minutes. An actual feeling of nausea was not always induced even when the gastric contractions were interrupted, and tone decreased. When a combination of prostigmine and atropine were given nausea did not occur. No undesirable side effects were noted (i.e. severe cramps, dryness, etc.). However, gastric motility continued and was not stopped even by severe stimulation or by inducing gagging. Nausea occurred only during gastric relaxation and hypomotility.—William D. Beamer.

PATHOLOGY

PEACOCK, P. R. AND BECK, S.: *Multiple mesenteric sarcomata in rats following ingestion of heated lard.* (*Brit. J. Exp. Path.*, V. 24, P. 143, Aug. 1943.)

Rats were maintained on a diet to which lard heated to 220° or 350°C. was added. Of 71 animals that survived 300 days or more, 4 developed multiple mesenteric sarcomata. No parasitic infestation was responsible for the sarcomas. If the diet to which the heated lard was added was restricted consisting of bread or potatoes and milk, there also developed benign gastropapillomatosis. The conclusion is reached that the heated fat develops a factor capable of inducing malignant mesoblastic tumors along the path of its absorption.—N. N. Underhill.

HARTMAN, F. W. AND ROMENCE, H. L.: *Liver necrosis in burns.* (*Ann. Surg.*, V. 118, P. 402, Sept. 1943.)

The substances commonly used to treat skin burns, such as tannic acid, silver nitrate, and other coagulants, may in themselves cause tissue injury. This injury is in addition to that known to be produced by the burn itself. By animal experimentation, the authors have shown that tannic acid wet packs are more likely to produce liver damage than tannic acid in the dry form or as a jelly. Silver nitrate and ferric chloride solutions were also found to result in a lower number of liver damage cases.—F. E. St. George.

ABELS, J. C., KUPEL, C. W., PACK, G. T., AND RHOADS, C. P.: *Metabolic studies in patients with cancer of gastrointestinal tract. XV. Lipotropic properties of inositol.* (*Proc. Soc. Exp. Biol. Med.*, V. 54, P. 157, Oct. 1943.)

Previously these authors had shown that the livers of patients with cancer of the gastrointestinal tract were infiltrated with fat. They also found that pa-

tients with gastrointestinal cancer had normal livers if they received lipocaic the night before laparotomy. Since lipocaic contains both choline and inositol in large amounts, and these are lipotropic by themselves, it became a question of which constituent of lipocaic was responsible. In this study on 10 patients with cancer of the gastrointestinal tract, it was found that the liver fat was reduced to one-half of that of a control group after the ingestion of inositol alone.—N. N. Underhill.

HANDLER, PHILIP AND BERNHEIM, FREDERICK: *The effect of choline deficiency on the fat content of regenerated liver.* (*Jour. Biol. Chem.*, V. 148, P. 649, 1943.)

Liver regeneration in partially hepatectomized rats proceeded rapidly in choline as well as mixed choline and thiamine deficiency and when the growth of the entire animal was depressed by the ingestion of excessive amounts of nicotinamide. While the regenerated livers of the choline deficient rats showed the usual fatty infiltration, the fat content of the regenerated livers of the choline-deficient rats whose growth was depressed by thiamine deficiency or by nicotinamide feeding was slightly below normal. It is suggested that the development of fatty livers in choline deficiency can proceed only when all other dietary factors will permit the growth of the whole rat rather than merely the growth of the liver. The effect of deficiencies of members of the vitamin B complex in preventing the appearance of fatty livers due to choline deficiency is the result of an impairment of the over-all metabolism of the rat rather than some specific defect in the metabolism of the liver.—Philip Handler.

CINELLI, A. P.: *Influence of ingested bile on the increase in blood phosphatase produced by biliary obstruction.* (*Rev. Soc. Argentina Biol.*, 18, P. 53, 1942.)

Six dogs had the common bile duct cut between 2 ligatures; 3 received by stomach tube 50-80 cc of bile daily. Blood phosphatase rose in all the animals in a similar manner; it was, therefore, not due to lack of bile in the intestine.—Courtesy Biological Abstracts.

METABOLISM AND NUTRITION

HANDLER, PHILIP: *The effect of simultaneous mineral and choline deficiencies on liver fat.* (*Jour. Biol. Chem.*, V. 149, P. 291, 1943.)

Young male rats on a low protein, high fat diet which was deficient in choline and minerals grew slowly for two weeks and at the end of that time had moderately fatty livers. In the following two weeks the animals declined in weight and the liver fat content returned toward normal. Choline-deficient animals given adequate amounts of mineral salts, but whose food consumption was restricted to that of the mineral deficient animals, continued to grow slowly and developed markedly fatty livers in the same period.—Courtesy Biological Abstracts.

BETHELL, FRANK H., BLECHA, ALMIRA AND VAN SANT, JEAN HASTINGS: *Nutritional inadequacies in pregnancy correlated with the incidence of anemia.*

(*Jour. Amer. Dietetic Assoc.*, V. 19, P. 165, 1943.)

Only a small number of 485 pregnant females in the rural North Central States met the present-day recommended dietary standards for pregnancy; the incidence of anemia was 25.4 per cent and the occurrence of hypochromic anemia and dietary deficiency of iron was correlated, also macrocytic anemia with inadequate protein intake. Dietary instruction significantly increased the protective foods eaten.—Courtesy Biological Abstracts.

OBERDISSE, K., AND FLECKENSTEIN, A.: *The influence of war-time diet on diabetes mellitus; the first one and three-quarter war years.* (*Deutsch. med. Wochenschr.*, V. 68, P. 717, 1942.)

A general beneficial effect on diabetes in war is due to diet rationing, particularly fat deficiency, which results in a decrease of total calories consumed. Of 47 patients with mild diabetes not requiring insulin, 39 showed less hyperglycemia; of 91 with moderately severe diabetes requiring insulin, 48 were improved and only 4 showed progress of the disease; but of 13 severe cases, only 5 were improved and 4 became worse. Dietary influences are most notable in diabetes of mild or moderate severity. Pre-war and present diabetic diets are presented in detail. There are sharp reductions in the amounts of protein and fat. Depot-insulin promotes better carbohydrate tolerance. Parallel findings are noted for the first world war, and mortality of males and females from diabetes in Prussia is figured in 1908-1938, with a nadir in 1919. Influences of age and sex on diabetes are also discussed.—Courtesy Biological Abstracts.

GREGORY, R. EWING, P. L. AND DUFF-WHITE, V.: *Effect of insulin, glucose, and glucose and insulin on the rate of metabolism of ethyl alcohol.* (*Proc. Soc. Biol. Med.*, 54, 206, Nov. 1943.)

Insulin and insulin and glucose have been used clinically in the treatment of acute alcoholism. However, the literature is in conflict on the question whether insulin, either alone or with glucose, increases the rate of oxidation of ethyl alcohol. The present study consists of 24 experiments on 6 dogs. Ethyl alcohol was given by vein, insulin subcutaneously and dextrose by stomach tube. Blood alcohol determinations were carried out repeatedly to the point where all the alcohol had disappeared. No evidence was found that insulin or insulin and glucose increases the rate of ethyl alcohol metabolism.—M. H. F. Friedman.

STETTEN, DEWITT, JR., AND GRAIL, GODFREY F.: *The rates of replacement of depot and fatty acids in mice.* (*Jour. Biol. Chem.*, V. 148, P. 509, 1943.)

Discrepancies in the earlier results of various investigators may have been due in some cases to the lack of essential dietary factors, notably pyridoxine and pantothenic acid, in the diets of the experimental animals. The animals in the present experiments were fed a high carbohydrate diet which included all the known essential B vitamins. For 5 days 7.5 per cent of fatty acid esters were added to this diet; these contained 10

atom per cent excess deuterium. One group was killed, while the others were returned to the diet without deuterio-esters and killed at intervals up to 14 days. The livers and carcasses were assayed separately for fats and isotope. Initially the liver fatty acids were more than twice as rich in isotope as the depot fat, but its concentration fell off much more rapidly. The half-times of the removal reaction were: liver, about 3 days; depot fat, about 6 days. The presence or absence of choline in the diet had little effect on the results.—Courtesy Biological Abstracts.

CHICK, H. AND CUTTING, M. E. M.: *Nutritive value of the nitrogenous substances in the potato, as measured by their capacity to support growth in young rats.* (*Lancet*, 245: P. 667, Nov. 27, 1943.)

Although the apparent digestibility of the potato is lower than that of wheat, the value of the nitrogenous substances in potatoes is somewhat greater for supporting the growth of young rats. Adding sodium citrate to the wheat to produce an alkaline ash did not change its value. A diet containing 9 per cent tuberin (the soluble protein in potato) was equal to one containing 11 per cent whole wheat protein, but was inferior to one containing 11 per cent casein. Milk protein is about 20 per cent superior to potato nitrogenous substances in supporting growth of young rats. The authors conclude that some portion of the non-protein nitrogenous substances complement the amino acids of the protein to produce a mixture of biological value not less than that of the protein itself.—William D. Beamer.

VINES, R. W. AND OLSEN, A. M.: *Cardiospasm with associated pellagra: report of case.* (*Proceed. Staff Meet. May Clinic.*, V. 18, P. 389, Oct. 20, 1943.)

Despite inadequate vitamin and calorie intake in conditions of cardiospasm, frank vitamin deficiency states are rare. This is in keeping with the recognized fact that vitamin deficiencies are less likely to develop among starving people than among people on poorly balanced diets. This may perhaps be explained in part by the lowered metabolism which accompanies starvation.

Cases of cardiospasm showing an associated pellagra are very rare. A case is presented of a 50 year old man with cardiospasm, extreme dilatation of the esophagus and marked pellagra. He was unable to eat solid foods and his weight decreased from 160 pounds to 100 pounds during the year. Approximately 500 milligrams of nicotinic acid amide was given intravenously each day. Striking improvement in the skin picture and in the patient's mental attitude was noted on the fourth day. Six days after vitamin therapy was begun treatment of the cardiospasm was instituted by means of hydrostatic dilatation. On discharge the patient could swallow everything without difficulty.

Vines and Olsen consider the possible role of vitamin deficiencies in the etiology of the cardiospasm. They discuss the possibility that cardiospasm and megacolon have a common etiology and discuss the symptomatic relief to be obtained from vitamin therapy.—F. X. Chockley.

An Explanation of Appetite^{*}

By

FREDERICK HOELZEL
CHICAGO, ILL.

Effect of a 33-day Fast

FASTING was primarily introduced in the study of the effect of variations in the protein intake on gastric functioning, on hunger and on appetite to serve merely as an alternative to simple protein restriction. The original intention was to include only short fasts but a 33-day fast became included because I took advantage of an opportunity to serve as a subject in a psychological study which called for prolonged fasting (16). Incidentally, it also seemed of interest to determine the effect of prolonged fasting on gastric functioning, as revealed by the technique used in this study, for comparison with the results of observations made during prolonged fasting in 1917 (2). The diet used during a few weeks before the 33-day fast in 1925 con-

cured earlier on other days. However, it should be noted that free acid was found in each of 21 aspirations, a peak volume of 90 cc. was attained (at 5:00 P.M.), the rate of secretion or of accumulation of the gastric contents was relatively high, bile was absent and inverse relations between acidity and volume are indicated, at least after the interruption in the observation period. In short, the general pattern of gastric functioning is more like that of March 20 (Fig. 1) than that of May 8 or May 9, (Fig. 1). The observation period was evidently terminated at 8:00 P.M. because of growing discomfort associated with the approach of a period of gastric contractions. It is obvious that the interval between the periodic gastric contractions be-

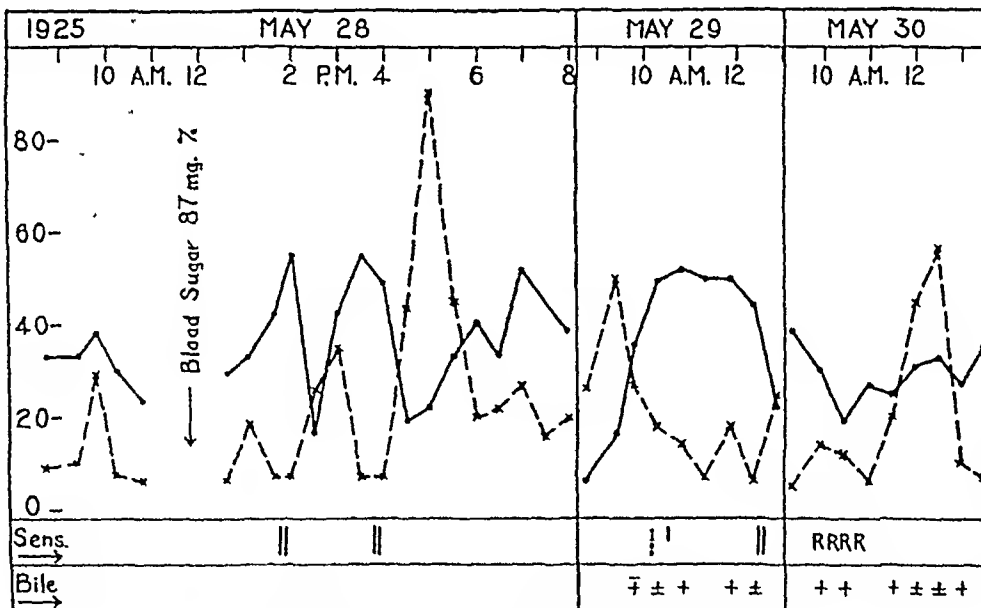


Figure 2—Showing gastric functioning during first 3 days of a 33-day fast.

tained a liberal amount of protein but on the day before this fast began the carbohydrate intake was made particularly high.

Figure 2 shows the results of observations on gastric functioning that were made during the first 3 days of the 33-day fast. The observation period on the first day of this fast, May 28, was interrupted during the morning when a blood sugar determination was made at the University of Illinois and the data secured late on that day (and also late on some other days) are not strictly comparable with data that were generally se-

came considerably prolonged during the last part of the observation period. A similar prolongation of the interval between periods, which incidentally included a peak of 135 cc. in the volume of the gastric contents, was observed after 5:00 P.M. on March 16 when 32 aspirations were made during a continuous observation period of 16 hours (between 7:00 A.M. and 11:00 P.M.). Seven distinct "hunger contractions" and more or less borborigmi were noticed at the end of the prolonged (5-hr.) secretory-motor period on March 16. More observations would nevertheless be needed to determine whether the gastric periodicity is generally prolonged in the later part of the day.

^{*} From the Department of Physiology, University of Chicago Chicago, Ill. (See first installment of this article in the March 1944 issue. It is completed in the present installment).

On the second day of the 33-day fast, May 29 (that is, after one day of fasting), the pattern of gastric functioning seems to have changed already to a type like that found on May 8 (Fig. 1) or after over two weeks of protein restriction. The acidity can be seen to have been sustained at a relatively high level during a large part of the time in spite of duodenal regurgitation. Epigastric tension was increased but gastric tonus appears to have been lower than on May 8—perhaps because of some fasting effects. Only two gastric contractions were felt—probably because the volume of the gastric contents was not reduced as much as on May 8 and duo-

denal regurgitation was already becoming a more prominent factor as a result of fasting. On the next day (May 30) only extreme restlessness was experienced during a period in which "hunger contractions" would very likely have been recorded by the balloon method of study. The restlessness appears to be explained by increased duodenal activity and perhaps also sensibility which is indicated by increased duodenal regurgitation. The restless period was followed by a period of general ease including gastric motor quiescence with an accumulation of secretions in the stomach. The rate of gastric secretion or accumulation seems to be already lower than it was on May 28. The commonly manifested inverse change in acidity and volume is not definitely indicated by the curves and this suggests that the gastric mucus secretion was not increased after the period of restlessness because no gastric contractions occurred which were felt. In other words, such occurrences support the view that the increase in mucus secretion which usually follows "hunger periods" is stimulated by mechanical irritation produced by the "hunger contractions" when they are also felt. The amount of mucus secreted would, however, depend partly also on the reserves for producing mucus. The desire to eat during restless periods like the one experienced on May 30 when no "hunger contractions" were felt was as

definite as during periods in which numerous contractions were felt. During such a restless period, it is difficult to think of anything but eating. But some food would also have been appreciated during the period of ease which followed the period of restlessness on May 30—after two days of fasting.

Figure 3 shows further changes in gastric functioning produced by the 15th and 20th days of the 33-day fast. The gastric acidity as well as the volume of the gastric contents can be seen to have been definitely decreased by the 15th day of fasting (June 11). A single gastric contraction was felt before a period of obvious

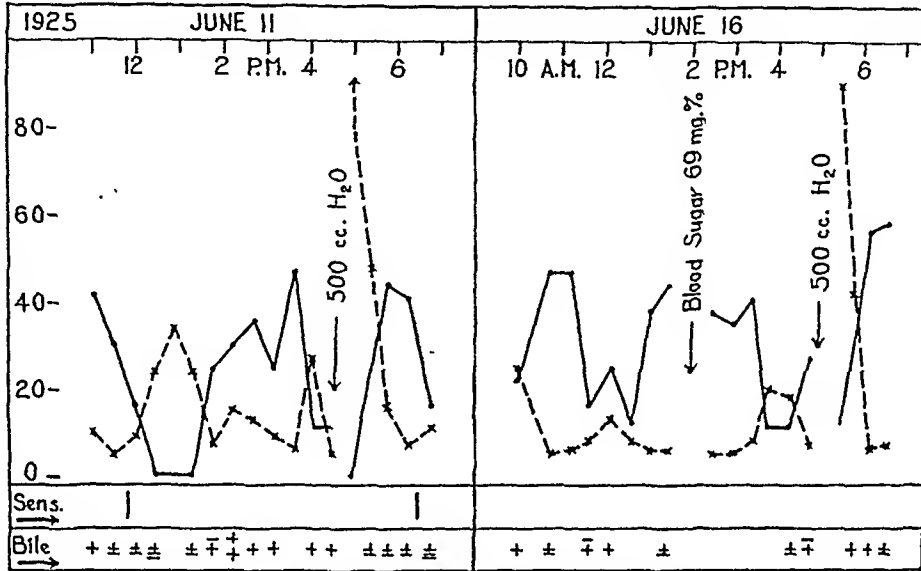


Figure 3—Showing gastric functioning and the effect of drinking water on the 15th and 20th days of fasting.

denal regurgitation was already becoming a more prominent factor as a result of fasting. On the next day (May 30) only extreme restlessness was experienced during a period in which "hunger contractions" would very likely have been recorded by the balloon method of study. The restlessness appears to be explained by increased duodenal activity and perhaps also sensibility which is indicated by increased duodenal regurgitation. The restless period was followed by a period of general ease including gastric motor quiescence with an accumulation of secretions in the stomach. The rate of gastric secretion or accumulation seems to be already lower than it was on May 28. The commonly manifested inverse change in acidity and volume is not definitely indicated by the curves and this suggests that the gastric mucus secretion was not increased after the period of restlessness because no gastric contractions occurred which were felt. In other words, such occurrences support the view that the increase in mucus secretion which usually follows "hunger periods" is stimulated by mechanical irritation produced by the "hunger contractions" when they are also felt. The amount of mucus secreted would, however, depend partly also on the reserves for producing mucus. The desire to eat during restless periods like the one experienced on May 30 when no "hunger contractions" were felt was as

motor quiescence during which the secretions accumulated in the stomach (about noon). An inverse change in acidity and volume is here manifested. Duodenal regurgitation or bile contamination of the gastric contents is further increased. On June 16, the average gastric acidity is somewhat higher than on June 11 but the average volume is lower. A notation on the original graph (for June 16) reveals that I felt quite well during the period between 2:30 P.M. and 4:00 P.M. in which no bile was found in the gastric contents. The effect of drinking 500 cc. of water was incidentally determined on June 11 and 16. A higher peak in gastric acidity would evidently have been found on June 11 if an aspiration had been made about 6:00 P.M. (between the 3rd and 4th aspirations following water drinking) but the results on June 16 and on some other days clearly showed that the acidity was increased by water drinking. One or more sharply felt "hunger contractions" were also always produced after the water (500 cc.) left the stomach.

Figure 4 shows the type of gastric functioning found between the 25th day and the end of the 33-day fast. A tendency to become more easily fatigued and a lack of interesting findings made the observation periods shorter toward the end of the fast. Low volumes and bile contamination of the gastric contents predominate.

Perhaps the pattern of gastric functioning during this period may best be described as tending to become disorganized on a diminishing plane of activity. A similar functional decline apparently occurs with aging. The fast was terminated after 33 days because water drinking then began to provoke some degree of nausea and it was thought that more prolonged fasting might make it difficult to retain food. However, the last two aspirations that were made before the fast was broken (at noon on June 30) showed that an appetite gastric secretion was stimulated by the preparation to resume eating and food proved to be well tolerated. About half

other days shortly after the fast when no water was taken before the gastric aspirations were made. In short, the gastric acidity was at first sharply increased as a result of re-alimentation after fasting. The volume of the gastric contents remained low at first but this was evidently due to a high gastric tonus and increased motility which tended to keep the stomach emptied in spite of increased secretory activity. The desire to eat became keenest about the fourth day after the fast was broken or at about the same time that the post-fasting gastric acidity became highest. With further re-alimentation, and particularly because of a relatively high

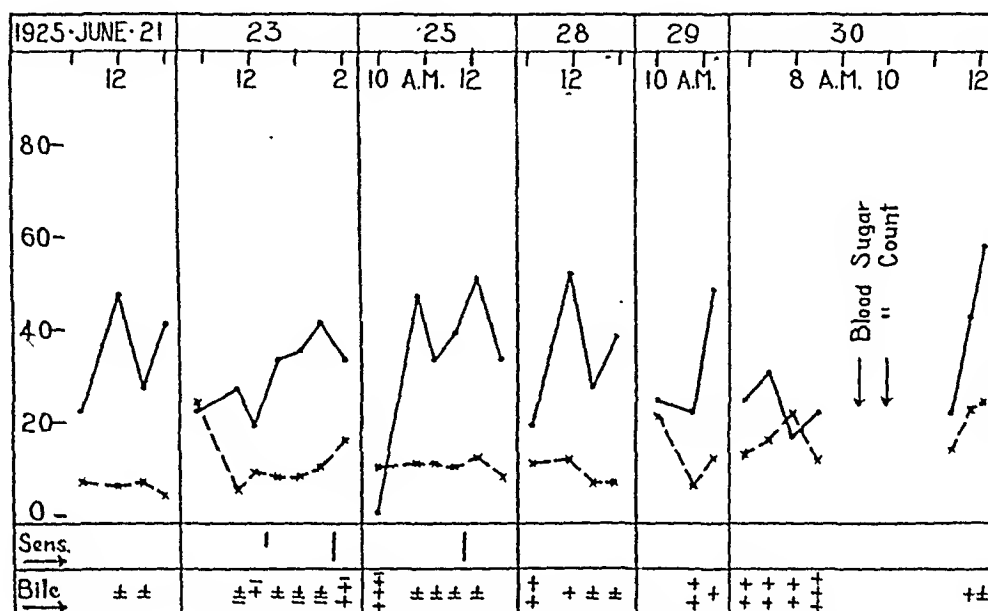


Figure 4—Showing gastric functioning between the 25th day and last day of a 33-day fast.

an hour after the reaction of the stomach was tested by taking some fruit juice, nearly 2 pounds of beef-steak were consumed—a little too much so soon after a prolonged fast. The result of the blood sugar determination which was made before the fast was broken was discarded as unreliable because it seemed to be too low (19).

Effect of Re-Alimentation After the 33-Day Fast

Figure 5 shows the effect of using a diet relatively high in protein, but occasionally restricted in total calories, during 34 days after the 33-day fast. One object after the 33-day fast was to determine whether it would be possible to recover completely from the fast in a period no longer than the fast. As a consequence the food intake became excessive on some days and this necessitated a restriction of the total intake on a few other days. The periods of observation on the "empty" stomach incidentally had to be made short to allow sufficient time for eating and digesting food. On the first day represented in figure 5 (July 2) some water was taken to relieve unusual thirst about an hour before the first aspiration was made. The volume of the gastric contents shows that the water had left the stomach but the water drinking may have made the gastric acidity a little higher than it otherwise would have been. However, the gastric acidity was nearly as high on a few

protein intake, the gastric acidity, tonus and motility were reduced and the average volume of the fasting gastric contents became increased, although the rate of gastric secretion probably again became somewhat diminished. "Hunger contractions" became vague and ceased to be of sufficient interest to be recorded after July 21. Similarly, bile contamination of the gastric contents, which had become extreme before the end of the fast, was promptly reduced by re-alimentation and did not seem worth being recorded after July 21. Recovery from the 33-day fast was apparently completed in less than 33 days. At least it then seemed that I was in better condition than before the 33-day fast began and I felt that another long fast could be undertaken immediately. Appetite and general gastro-intestinal functioning after the fast obviously served to promote a sufficient intake and utilization of food to insure full recovery in so short a time. In fact, the chief difficulty before recovery became practically completed was to avoid over-eating.

Effect of a 41-Day Fast

The effect on gastric acidity of re-alimentation with a diet high in protein after the 33-day fast raised the question concerning what the effect would be of the use of a diet low in protein after a prolonged fast. To help answer this question and also for other reasons, another

prolonged fast, which lasted over 41 days (1001 hours), was begun 34 days after the 33-day fast was concluded. Figure 6 shows the results of observations made during the first 3 days of this fast. The protein intake was forced more or less on the day before this fast began while the carbohydrate intake was similarly forced before the 33-day fast began. The practice of forcing food (eating as much as possible without overtaxing one's capacity) in anticipation of fasting served partly as a means of making it easy to start a fast on an intended day, as there would be little desire to eat on the first day after a practically excessive food intake.

activity (mainly mucoid). Periodic changes in motor activity or in an otherwise relatively low gastric tonus nevertheless occurred. On the basis of about 500 earlier tests in which both the free and total acidity of the fasting gastric contents were determined, it can be said that a periodic change in bound acid, inversely related to volume, occurred whenever free acid was absent. Complete anacidity was never found and total acid was not determined after about 500 tests because the bound (fasting) acid was found to be practically uniform when free acid was present. On the second day of the 41-day fast (Aug. 4) or about 16 hours after the end

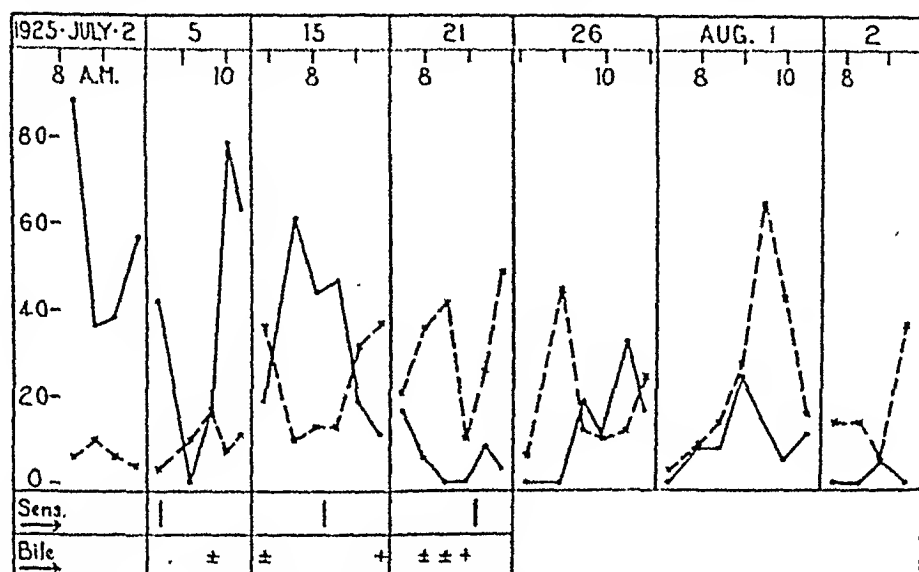


Figure 5—Showing the effect on gastric functioning of re-alimentation with a diet high in protein after 33 days of fasting.

In any case, one result of this forced pre-fasting high protein intake was that no free acid was found in any of 14 aspirations made on the first day of this fast (Aug. 3). This contrasts sharply with the finding of free acid in all of 21 aspirations made on the first day of the 33-day fast. It should incidentally be borne in mind that the findings on the first day of the 41-day fast represent the extreme of effects on gastric functioning already illustrated in figure 5 and do not represent the effect of a high protein intake on only one day. As indicated in figure 6, the first aspiration which was attempted at 9:00 A.M. on Aug. 3 showed that some food residues were still in the stomach. Hence, no attempt was made to determine the volume of the gastric contents at that time or at 10:30 A.M. when the food residues were found reduced. The absence of free acid while traces of food were present, as well as after all traces of food disappeared, illustrates a close relation which was generally found between the levels of gastric acidity during digestive periods (about 200 aspirations) and during interdigestive periods (over 2000 aspirations) during 1925-1926. In short, the interdigestive, basal, spontaneous, continuous or fasting gastric secretion is an index of the potential digestive secretion. The curve representing the volume of the gastric contents Aug. 3 indicates a sluggish gastric secretory

of the observation period on the first day, some free acid was found. On the next day (Aug. 5) free acid was also found and the rate of gastric secretion appears to have been increased. It should however be noted that the gastric aspirations on Aug. 5 were made later in the day than on Aug. 4 but not later in the day than on Aug. 3.

Figure 7 shows the findings on the 15th, 23rd, 32nd, and last days of the 41-day fast. They are similar to the findings during corresponding parts of the 33-day fast (Fig. 3 and Fig. 4). Bile contamination of the gastric contents again became conspicuous and slight nausea was finally also provoked by the mere drinking of water. On the last day of the fast, the increased acidity at "A" suggests that an appetite gastric secretion was stimulated after I announced my intention to break the fast. The preparation of some food began at "B" and the fast was broken at 3:30 P.M. (Sept. 13).

This fast proved to be less of an ordeal than the 33-day fast. Warmer (summer) weather and a somewhat lower gastric acidity evidently helped to make the fasting easier but it is also obvious that a fast of 41 days could hardly have been tolerated if I had not recovered fully or more than fully from the 33-day fast in the 34 days between the two fasts.

Effect of Re-Alimentation After the 41-Day Fast

After the 41-day fast a diet low in protein was used to determine whether the gastric acidity would become higher than after the 33-day fast when a diet high in protein was used. From earlier personal experiences it was known that severe edema might develop with the use of an ordinary diet low in protein after fasting but it was then thought that edema could be prevented by simultaneously restricting the salt (NaCl) intake. Hence, both the salt and protein intakes were restricted during the first 14 days after the 41-day fast. Edema nevertheless developed. The gastric acidity promptly rose

adding salt to the diet before liberalizing the protein intake. As previously reported (8, 12), added salt sharply increased the gastric acidity and made it higher than at any time after the 33-day fast, as well as higher than at any other time in which the gastric acidity was determined during 26 years (2, 8, 13). As a result of this increase in gastric acidity and also gastric or gastroduodenal sensibility, the further prolongation of protein restriction became practically intolerable. Enormous amounts of meat were then eaten and appreciated and the gastric acidity consequently again became rapidly reduced (8, 12).

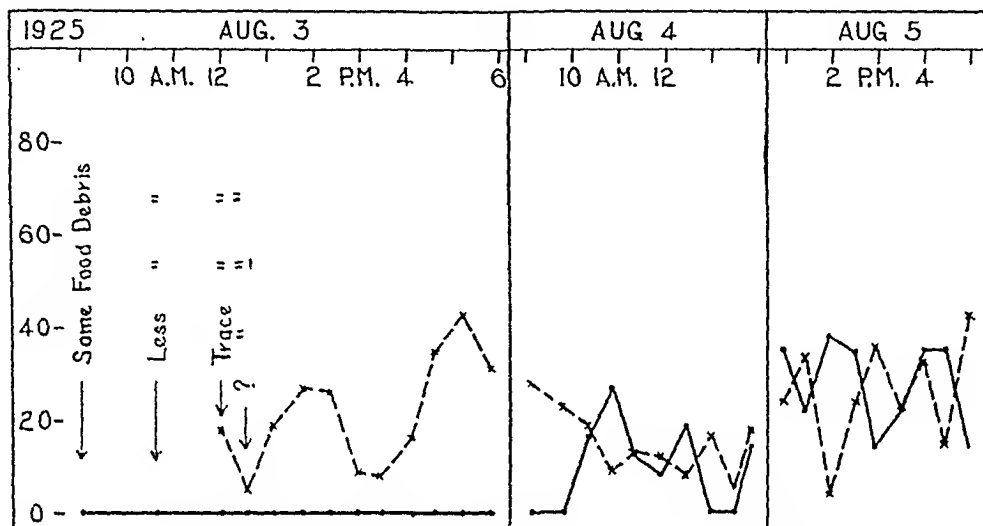


Figure 6—Showing gastric functioning during the first 3 days of a 41-day fast.

above the levels observed during the fast but it did not become as high as the peak in acidity after the 33-day fast. This experience and observations made on another occasion when gross edema was manifested left the impression that an edematous condition tends to keep the gastric acidity more or less depressed or decreases the production of HCl in the stomach. However, it now seems that this is the case only when an NaCl deficiency has been created. A transient NaCl deficiency can apparently be created even without a restriction of the salt intake by the increased need of the organism for salt when hydration increases, and hydration evidently increases after sufficient protein starvation in spite of NaCl restriction when the carbohydrate intake and possibly also the intake of some minerals other than NaCl is high enough. During the period of NaCl and protein restriction after the 41-day fast, the attempts to satisfy intense hunger in spite of these restrictions led to the use of some foods like turnip tops and carrot tops which were never eaten under more normal circumstances. Such foods were greatly appreciated at this time but they probably supplied the minimum of minerals that appear to be necessary to make the development of edema possible. An NaCl deficiency however seemed indicated by the fact that the desire for salty food became almost as great as the craving for protein-rich foods at this time. In any case, a keen craving for salt was probably as great a factor as rational considerations in leading to the decision to try

An interrelation is here indicated between nutritional hydration, salt-hunger, HCl production and protein-hunger. That is, a protein deficiency tends to promote the development of edema or increases hydration which creates salt-hunger or increases the appreciation of salt. When the desire for salt is satisfied, the gastric acidity is increased and this apparently creates protein-hunger or increases the appreciation of protein-rich foods. After protein-hunger is satisfied, the edema or hydration produced by a protein deficiency is remedied. Obviously, a self-regulating mechanism such as this can be expected to function well only within certain limits. In any event, it has recently become clear (13) that edema-like hydration following fasting plays a physiologic role in modifying basal gastric functioning and appetite so that the type of food intake is promoted which serves to eventually restore the normal nutritional state and the normal pattern of basal gastric secretory and motor functioning.

Effect of Different Sources of Protein

In the study of gastric functioning and appetite, meat (chiefly beef, veal and fish) was used as the main source of protein until after the period of re-alimentation which followed the 41-day fast. Meat was used because, in personal experience, it served best to satisfy the appetite for protein. This satisfying effect seemed to be due to its power to reduce gastric acidity or (physiologic) hyperacidity produced by protein restriction. It therefore seemed of interest to find out wheth-

er the less satisfying value of other sources of protein could be explained by differences in their power to reduce gastric acidity or hyperacidity. Hence, during separate periods, the value of using either eggs, cheese or vegetable sources of protein (nuts, beans and wheat gluten flour) was determined. When eggs were used, separate tests were made of the value of egg-white and egg-yolk. In one period, the value of using meat in moderate amounts or with the total calorie intake reduced was also determined as excessive amounts were often used earlier in the study. In this connection, from 5 to 9 half-hourly determinations of the acidity and

averages of the 5 to 9 determinations that were made daily. The curves of acidity and volume show general inverse changes but it is obvious that the changes in acidity were much greater than the changes in volume. This is due to the fact that the protein and carbohydrate intakes often changed inversely while the total calorie intake generally remained relatively constant. As a consequence, most of the changes in the food intake affected the acidity in the same direction but affected the volume in opposite directions or tended to keep it relatively constant. Nevertheless, exceptions to the general inverse relationship between the protein in-

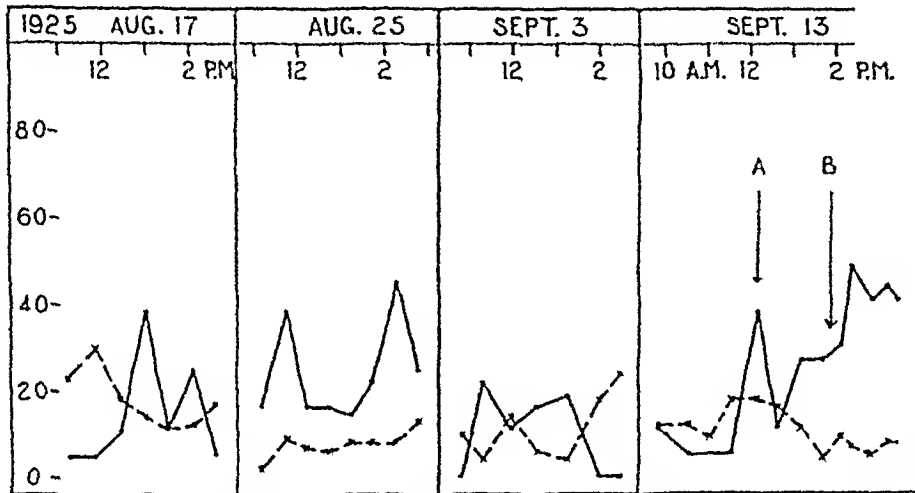


Figure 7—Showing gastric functioning on the 15th, 23rd, 32nd and last day of a 41-day fast.

volume of the gastric contents were made every morning between Nov. 1, 1925 and Jan. 29, 1926.

In the earlier report on the effect of variations in the protein intake on gastric acidity (8), the protein, fat and total calorie intakes, as well as the gastric acidity, during this period were shown graphically but the incidental carbohydrate intake and the volume of the gastric contents were neither shown nor considered to be of significance. This, as explained in the first part of this paper, constituted a major error in the earlier work but, at that time, it seemed of importance only to show that changes in the fat intake did not account for the changes in gastric acidity that were attributed to the variations in the protein intake. The total calorie intake was shown only as evidence that the gastric acidity could be reduced without an excessive meat or total food intake. Since then, however, it has become clear that total calorie restriction or undernutrition also reduces gastric acidity like a high protein intake but the effect of undernutrition on gastric acidity seems to be due to a reduction of the carbohydrate reserves and corresponding hydration (12, 13). This might have become evident already in the earlier study if the carbohydrate intake and the volume of the gastric contents had been taken into consideration as in figure 8.

Figure 8 shows the gastric acidity and protein intake, as well as the carbohydrate intake and the volume of the gastric contents, during the period under consideration. The represented acidities and volumes are the

take and incidental carbohydrate intake explain some of the observed differences in the effects of the use of proteins from different sources. Thus, egg-white, which was used in the coagulated form (excepting on one day when it was used raw, produced diarrhea and led to a rise in gastric acidity), at first seemed to have no value in reducing gastric acidity but the associated carbohydrate intake, as indicated in figure 8, was then very high. Later, the associated fat intake was increased to make the fat intake with the egg-white more nearly like that involved in using egg-yolk. As the total calorie intake then remained relatively constant, the increase in the proportion of fat in the diet served to reduce the incidental carbohydrate intake and hence also the gastric acidity. During the period in which meat and fish were used, the decrease in gastric acidity was evidently partly due to the low carbohydrate intake, which was then due to a restriction of the total calorie intake. The failure of nuts (plus beans on one day) to reduce, or check a rise in, gastric acidity seems explained by the high carbohydrate intake which the use of such sources of protein involves. The effectiveness of gluten flour (80% gluten) in reducing gastric acidity was very likely due to the very high (but relatively unpalatable) protein intake and the reduction of the incidental carbohydrate intake that its use made possible. The use of cheese (mainly creamed cottage cheese) involved a much higher carbohydrate (and fat) intake than when meat and fish were used but my impression

was that the lactic acid in cottage cheese also had a specific effect in preventing a sharp reduction in gastric acidity. The cottage cheese left the stomach rapidly and had a general laxative effect although it did not produce diarrhea. The lowest level of acidity at the end of, or immediately after, the cheese period was due to the trial of limburger cheese on the last day of the cheese period but it was not the direct or exclusive effect of the protein intake. Limburger cheese was tried because of a claim that it had a low fat content (as prepared in Europe). However, the limburger cheese used (a Wisconsin brand) was later found to have a fat content as

take. Diuresis and excessive salivation were produced and the gastric acidity rose somewhat but not as sharply as on the occasion when a high salt intake was tried after salt restriction following the 41-day fast. However, the general state of nutrition also differed considerably on the two occasions.

THE HEARTBURN DUE TO THE USE OF SUGAR DIETS.

At the beginning of this paper, the development of heartburn as a result of using mainly sugars as food was referred to. It should be obvious that an increase

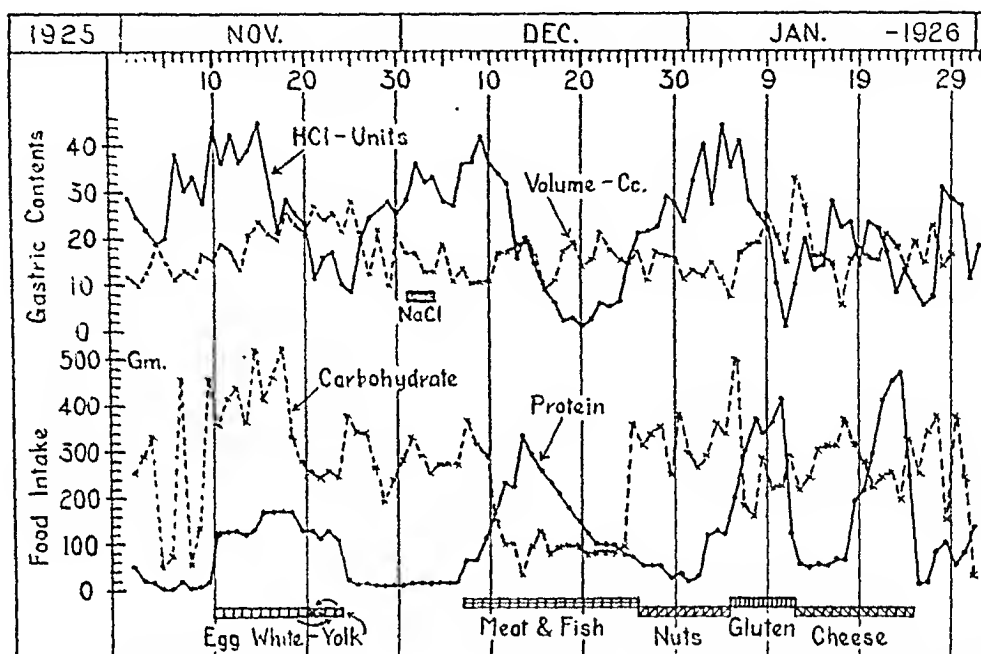


Figure 8—Showing the effect of variations in the protein and carbohydrate intakes (lower curves) and of different sources of protein on the acidity and volume of the fasting gastric contents (upper curves).

high as most other types of cheese. The large amount of limburger cheese used produced an apparent toxemia or bacteremia which was responsible for the lowest depression in the gastric acidity. The toxemia or bacteremia cleared up and the gastric acidity rose again after about 48 hours but the depressed physical state produced in this experience discouraged immediate further experimentation involving nutritional extremes.

The results suggest that the preference for meat (including fish and fowl) as a source of protein is largely due to the possibility of using it "to hit the spot" without the necessity of incidentally consuming large amounts of carbohydrate and fat. Superior digestibility, satisfactory amino acid content, suitable physical characteristics, good acid binding power and taste (in the prepared forms) are evidently other factors. However, when the gastric acidity tends to be low, cheese, eggs or vegetable sources of protein may be preferred because their use would not be as likely to tax or reduce the gastric acidity further like the use of meat.

During the first few days in December (Fig. 8) a high salt intake (about 20 grams on each of 3 successive days) was tried after 7 days of salt restriction and with salt restricted another 7 days after the high in-

in gastric acidity due to the incidental restriction of the protein intake was one factor in the development of the heartburn. However, another factor seems to be the effect of sugar or a high carbohydrate intake on gastric tonus, particularly on the tonus of the cardia. In eating candy after my main meal of the day in recent years, it was observed that the candy is generally appreciated until enough has been consumed to provoke a belch. It does not appear that reverse peristalsis (beginning in the duodenum) or nausea is here involved. The cardia simply seems to relax sufficiently to permit an escape of the swallowed air or gas in the stomach. This seems to be a physiologic consequence of a completely satisfying carbohydrate intake which explains the custom of Arabs and Turks, for example, to show their appreciation of a meal by belching. The Arabian and Turkish custom probably originated because of the effect of the liberal use of figs and dates in the diet but the bread eating Bavarian peasants also used to belch vociferously in appreciation when their stomachs were full. If, at such a time, the gastric acidity is within moderate bounds because of an adequate protein intake, the belching would not be likely to produce heartburn but, if the acidity is high and the acid is not bound, as when

an exclusive sugar diet is used, enough acid is likely to enter the esophagus with or even without belching to produce heartburn.

BUCCAL FACTORS IN APPETITE

Although the evidence presented in the foregoing emphasizes the importance of gastric or gastro-duodenal factors in appetite, the fact remains that we are mainly aware of the appreciation or lack of appreciation of food (and water) in the mouth. In the mouth region, taste, smell, mucosal (tactile and other) sensibility, salivation and the swallowing impulse are involved. Undoubtedly, foods are most intensely appreciated when they appeal particularly to taste and smell but taste and smell merely seem to be the "last courts of appeal." Relatively bland foods are appreciated when appetite is keen and this appreciation appears to be largely independent of taste and smell. It seems more like the appreciation of water when very thirsty. In any case, my impression is that the appreciation of bland proteins, fats and starches is due to their effect in combination with saliva, on the buccal mucosa. Appreciation by the mucosa is presumably mediated mainly through the sympathetic nerves and is therefore "instinctive." We thus "know" what we like without knowing precisely why or how we like it. We become aware of the salivary response and the tendency to swallow whatever is appreciated. We also observe the incidental flavor or aroma of the food and thus taste and smell become important factors in an acquired appetite. But the fundamental appreciation of food or basal appetite depends on need and on condition, particularly the condition or readiness of the digestive tract to use food. Carlson drew a similar conclusion already in 1916 (5).

COMMENTS

In this study, only a rough analysis of the effects of some variations in the protein, carbohydrate, salt, water

and total calorie intakes on gastric functioning and appetite was made and mainly at the age of 36. A great deal of additional study will be needed concerning the effects of variations in the food intake on appetite (including salivation and the composition of saliva) in the two sexes, in individuals differing in constitution (particularly in regard to the weight level attained or maintained), in cases of anacidity, at different ages and under various other conditions.

Anyone sufficiently interested can study some aspect of appetite on himself. For making gastric aspirations, a perforated soft rubber tube with a lead sinker tied in the end and costing less than 10 cents was preferred in my study to special stomach tubes and tips that were also tried. The knack of introducing or swallowing a tube with ease can very likely be acquired by most individuals by practicing at first with the end of the tube coated with a little syrup or with anything else that will promote swallowing.

SUMMARY

In a self-study of appetite, particularly the appetite for protein-rich foods, it was found that the basal gastric or gastro-duodenal secretory and motor activity as well as epigastric sensations varied with the protein intake or reserve. The involved relations to protein needs seem to explain the physiologic regulation of the protein intake. It was further found that the protein, carbohydrate, salt and water intakes or reserves are interrelated in affecting basal gastro-duodenal functioning and appetite. Buccal factors in appetite are affected by changes in nutrition in parallel with the gastro-duodenal factors but the common reference of the appreciation of food mainly to taste and smell merely seems to be due to a greater awareness of the flavor and aroma of foods than of the more basic satisfying characteristics of relatively bland food constituents, such as, many proteins, fats and starches.

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The Role of The Fat Soluble Vitamins A and D in Nutrition

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FOREWORD

THERE are a number of reasons for including a study of the present status of both vitamins A and D together in nutrition. In the first place, they are both fat soluble vitamins. Secondly, their absorption from the alimentary tract is influenced to a considerable degree by those factors which interfere with fat absorption generally. Thirdly, they both occur not uncommonly in combination in natural sources. Their extremely important role in nutrition is of course unquestioned.

An attempt has been made to outline the major role that these two fat soluble vitamins have achieved in the field of nutrition. For the most part only those facts have been presented that have stood the test of time and have achieved general recognition. Contributions of a controversial character which still remain primarily in the field of speculation have received only passing mention or have not been included.

The generally accepted facts about vitamins A and D are in themselves contributions of a sufficiently brilliant character and indicative of the march of medical progress in the field of nutritional research.

EARLY HISTORY OF THE ROLE OF VITAMINS IN NUTRITION

There are two main groups of alimentary constituents. In the first group are those substances which yield energy as well as the building stones for the creation of tissue. In the second group are the protective substances. Vitamins belong to this second group. They yield neither energy nor do they enter into the chemical structure characteristic of the living cell, yet without their presence such transformations of food into energy or structure are impossible. They are organic compounds essential for growth and function. They therefore make possible by their presence the transformation of energy as well as the metabolism of the living cell.

Evidence of the existence of vitamin deficiency states is to be found in the writings of antiquity. The skeletons of prehistoric man show changes which resulted from a deficiency of vitamin D (rickets) as well as a deficiency of vitamin C (scurvy).

By the middle of the sixteenth century, the value of the juice of orange and lemon was discovered as a cure of scurvy. Somewhat later the value of fresh vegetables was discovered as an anti-scorbutic. These remedies were finally popularized by Lind in 1757.

It is interesting to note that the earliest attempt to treat successfully what is now recognized as a vitamin deficiency state (lack of vitamin A) was in the use of therapeutic measures to counteract night blindness. The livers of goats were recommended for this condi-

tion by the old Greek, Roman and Arab physicians. The ancient Hebrews recommended fish bile for this condition.

Further evidence of the value of fish livers is to be found in the writings of the middle ages and the use of fish liver oils was later strongly recommended by Schlutze in 1824. Additional evidence linking night blindness with faulty nutrition is to be found in the work of Hoefer (1657) and Von Bergen (1754).

As will be more fully elaborated later, modern clinical and experimental procedures have verified fully the value of liver and particularly of fish liver as an excellent source of vitamin A.

The original belief was that certain foods exerted their beneficial effect by overcoming toxic material present in the organism which was the actual cause of the disease. It was only later that the concept arose that it was an absence in the dietary of a substance essential to the life process which was responsible for the nutritional disorders. Thus when the diet consisted of proteins, fats, carbohydrates, water and minerals, the animals died. Numerous experimental efforts were made which eventually proved that the life of an animal was impossible if fed only with the dietary constituents then recognized. Lumin, however, showed that when fresh milk was added to the same diet the animals survived. This experiment indicated that in addition to the recognized constituents of the diet, there were unknown substances without which life was impossible.

In 1897 came the epoch making report of Eijkman who proved experimentally that beri-beri was due to a food deficiency present in the rice bran and that this substance capable of curing the disease could be extracted from the bran by means of water or alcohol. This was followed by the work of Holst and Frolich in 1907, who demonstrated experimentally that scurvy was similarly a food deficiency disorder.

Eventually the name vitamin was given to these compounds. (Funk, 1912). Ultimately, as is well known, many more vitamins were discovered and their chemical nature established. In many cases the artificial synthesis of these vitamins was thus made possible.

The first experimental evidence of the importance of a fat soluble substance in the maintenance of normal nutrition was that of Steppe in 1909. He subjected milk-bread to extraction with alcohol and ether. When mice were fed on this extracted bread, they died. If, however, the extracted material was fed with the bread, the mice showed normal growth. Evidently a substance soluble in both alcohol and ether had thereby been removed, essential to life itself.

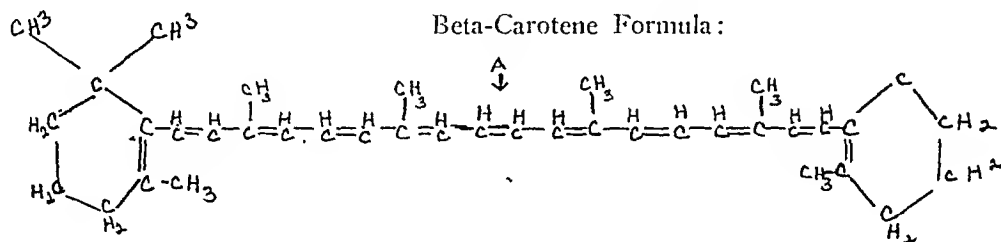
Hopkins in 1912 showed the importance for the

Examination showed the persistence of unchanged carotene in the alimentary tract indicating that the change to vitamin A did not occur in the course of digestion but that it took place after the absorption into the blood stream.

To show the importance of the liver as the organ in which the conversion of carotene to vitamin A took place he quoted the work of Buckley (1930) who noted that in cases of parenchymatous degeneration of the liver in cattle, this organ had a deep yellow color due to the excessive amount of carotene. When chemically treated, large amounts of crystalline carotene were obtained. Since large amounts of vitamin A are normally present in the liver oils of cattle and only traces of carotene, the pathologic condition of the

the necessity of converting carotene into vitamin A.

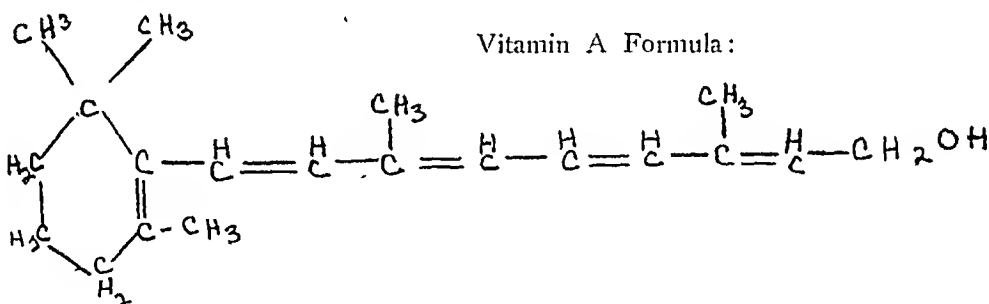
A number of scientific investigators were perplexed by the fact that the yellow-red plant pigment, carotene, exhibits vitamin A potency although the vitamin A of fish liver oils is colorless. Palmer (*Palmer, L. The Chemistry of Vitamin A and Substances Having a Vitamin A Effect. J. A. M. A. 110:1748, 1938*) showed that of the yellow pigments in plants there were four that could be converted into vitamin A, namely, alpha, beta and gamma carotene and cryptoxanthin. In the process of conversion to vitamin A, these yellow pigments become almost colorless. The manner in which this change occurs chemically is shown by the following formulae as demonstrated by Karrer in the transition of plant carotene to the vitamin A of fish liver



liver was evidently the etiologic factor in the failure of the conversion of carotene to vitamin A. Another evidence of the role of the liver in this process is the fact that most of the vitamin A is to be found in the

oil.

In the liver there is a hydrolytic process which breaks up the formula into identical molecules of vitamin A of the following chemical structure:



liver and only comparatively small quantities are present throughout the rest of the body. The liver is therefore not only the organ primarily concerned with the conversion of carotene to vitamin A but it is also the essential storage plant for this vitamin.

This conversion of the provitamins A to vitamin A is believed to be caused by an enzyme, carotenase, apparently primarily in the liver (*Olcott, H. S. and McCann, D. C. Carotenase. Transformation of Carotene to Vitamin A in Vitro. J. Biol. Chem. 94:185, 1931*). Olcott and McCann showed that carotene could be changed to vitamin A by incubating it with fresh liver tissue or with an aqueous extract of liver. They considered the agent responsible for this change to be an enzyme since it was destroyed by heat.

There is considerable variation in the ability of various carnivorous animals to convert the provitamins A into vitamin A. Fortunately carnivorous animals ingest a sufficient quantity of vitamin A containing foods so that they are essentially independent of

Alpha and gamma carotene and cryptoxanthin however are supposed to produce only one molecule of vitamin A from each molecule of the provitamin. This is due to the difference in chemical structure of these particular provitamins.

If the formula of vitamin A is studied it is noted that it has an alcohol group ($-CH_2OH$), resulting from retention of part of the water in the hydrolytic cleavage of beta-carotene. This alcohol group is capable of forming esters when another organic group replaces the OH group. The variation in fish oils from the standpoint of vitamin A potency is in part attributable to the presence of the ester form instead of the alcohol group.

Although the chemical relations involved in the change from the carotenoids to vitamin A have been shown, the reverse procedure, namely, the conversion of vitamin A to carotene has not been accomplished.

Vitamin A is apparently the only vitamin which occurs as a result of animal metabolism, although the

provitamins are entirely the result of plant metabolism.

The conversion of the provitamins, carotene and cryptoxanthin, into vitamin A in the liver occurs through the intermediary of an enzyme as previously stated. The thyroid gland may also play a role in this process. Some of the experimental evidence to sustain this claim has been obtained on thyroidectomized goats. Under normal conditions with the thyroid intact, the goat converts carotene to the colorless vitamin A and the milk produced is white in color. When the thyroid has been removed, the milk is yellow in color.

Further evidence suggesting a relationship of the thyroid to the ability of the organism to convert carotene to vitamin A is shown in the work of Clausen and McCoord (*Clausen, S. W. and McCoord, A. B. The Carotinoids and Vitamin A of the Blood, J. Pediat. 13:635, 1938*). They found that large amounts of thyroxin lowers the vitamin A content of the liver. In most cases of hyperthyroidism, the plasma carotene showed high values. The vitamin A content of the plasma, however, was low in all cases.

Besides vitamin A which is found only in salt water fish and mammals, other similar substances have been described such as vitamin A₂ (*Edisbury, J. R., Morton, R. A. and Simpkins, G. W. Possible Vitamin A₂, Nature. 140:234, 1937*). Vitamin A₂ is present in fresh water fish in addition to vitamin A. Small amounts of Vitamin A₂ however have been found in halibut liver oils in addition to vitamin A. It is rarely demonstrable in cod liver oils and was never detected in whale liver oils.

Vitamin A₂ has not been isolated in pure form nor has its exact chemical constitution been determined. Evidence, however, of the relationship of vitamin A and vitamin A₂ is to be found in the fact that when carotene is fed to fish such as the perch, both of these vitamins are synthesized, thus indicating that carotene is also a precursor of vitamin A₂ (*Morton, R. A. and Creed, R. H. Conversion of Carotene to Vitamin A₂ by Some Fresh-water Fishes, Biochem. J. 33:318, 1939*).

There is no evidence according to Wormal (*Wormal, A. Annual Reports On the Progress of Chemistry for 1938, 35:332, 1939*) that vitamin A₂ plays any significant role in the nutrition of the mammal although biologically it may be the equivalent of vitamin A₁. Experimentally it has been shown that the livers of rats fed with a concentrate containing vitamin A₂ will on examination be found to contain this vitamin.

A method of distinguishing between vitamin A and A₂ has been recommended by Greenberg and Popper (*Greenberg, R. and Popper, H. The Differentiation Between Vitamin A₁ and A₂ Fluorescence Microscopy. Proc. Am. Physiol. Soc., 129:367, 1940*) and depends on the variation in the nature of fluorescence of the two. Thus vitamin A shows a green fluorescence and vitamin A₂ exhibits a reddish fluorescence. They found that in salt water fish a considerable amount of this

green fluorescence characteristic of vitamin A was demonstrable in the fat droplets of the epithelial cells of the liver. When exposed to ultra violet irradiation, this characteristic green fluorescence fades. A similar condition is to be found in the mammal. In the livers of fresh water fish, the green fluorescence is absent but in its place one can demonstrate a yellow-brown fluorescence distributed in a similar manner. This also fades on irradiation with ultra violet light. Fluorescence microscopy therefore offers not only a means of distinguishing between vitamin A and vitamin A₂ but also enables us to determine the distribution of the two vitamins in various potential sources and demonstrates the fact that vitamin A is present in the livers of salt water fish, while vitamin A₂ is to be found in the livers of fresh water fish. Since it is the vitamin A that plays the predominating role in mammalian physiology, it indicates the importance of such a source as halibut liver oil coming from a salt water fish. When vitamin A was fed to the rat, fluorescence microscopy was able to demonstrate its presence within the lumen of the stomach and also within the lumen and the wall of the small intestine. From there vitamin A could be traced by way of the epithelial lining and lymphatics to larger lymphatics, the main area of absorption being in the jejunum. Within several hours after feeding vitamin A to rats showing a deficiency state, the green fluorescence could be demonstrated in the Kupffer and adjacent epithelial cells of the liver as well as in the adrenal glands and ovaries.

The origin of the precursors of vitamin A is to be found in plants, chiefly as carotene. These are obscured by the green coloring matter of the plant, the chlorophyll. Although there are apparent exceptions, there is a fairly parallel relationship between the richness in carotene, and the amount of chlorophyll formation in green leaves. Following the ingestion of green leafy substances, the carotenes which they contain are altered by the body into vitamin A. What is promptly needed reaches the tissues of the body, and the excess is stored. Chickens and cows are able to transform the provitamins of grasses unfit for human consumption into vitamin A containing foods, which form good sources of this vitamin in an excellently assimilable manner, namely eggs and milk. Good sources of vitamin A are therefore to be found in green leafy and yellow vegetables, eggs, milk and milk products, such as butter, cream cheese and ice cream.

The most important source of vitamin A is in the oils obtained from liver. This is so because the excess of vitamin A in the animal organism is stored mainly in the liver.

The exact origin of the large amounts of vitamin A in fish livers is not clearly understood. Many species of fish ingest plankton which though devoid of vitamin A may contain its precursors. These then may be transformed into vitamin A, and stored mainly in the liver. The huge reserves of vitamin A present in fish may also be due to the fact that they are able to utilize astaxanthin which is the predominant pigment in the minute crustacea which are consumed in enormous

amounts by fish. Astaxanthia appears to be closely related to vitamin A and fish may possess the peculiar power of utilizing this substance and converting it into vitamin A. Whatever the method of transformation, the important fact is that the fish liver oils are an excellent source of the fully synthesized vitamin A (Morton, R. A. *The Constitution and Physiological Significance of Carotene and Allied Pigments. Chemistry and Industry* 59:301, 1940).

Vitamin A can be readily isolated from the liver oils by means of the vacuum distillation process. It was finally crystallized. (Holmes, H. N. and Corbet, R. E. *The Isolation of Crystalline Vitamin A. J. Am. Chem. Soc.* 59:2042, 1937). Isolated crystalline vitamin A from fish liver oils appears as pale yellow needles. A biologic assay of the crystals of various fish liver oils showed variations between about 2,000,000 and 3,000,000 International Units per gram. It is destroyed by ultra-violet light. It is fat-soluble but insoluble in water.

Vitamin A heated in the presence of oxygen becomes inactivated. Oxidation processes generally cause a reduction in the physiologic activity of the vitamin. Therefore to insure the retention of vitamin A potency in commercial preparations, methods are employed to prevent oxidation. Various antioxidants may therefore be added to the vitamin A preparations or in the case of fish liver oils, they are sealed in vacuum.

The color test of Carr and Price (Carr, F. H. and Price, E. A. *Colour Reactions Attributed to Vitamin A. Biochem. J.* 20:497, 1926) is ordinarily employed for the determination of vitamin A. To a solution of vitamin A in chloroform is added a 20 to 25% solution of antimony trichloride in chloroform. A blue color develops which reaches its maximum intensity in ten seconds and then begins to fade promptly. The color is measured in a colorimeter and the value may then be checked against a standardized solution of copper sulphate. Values obtained in this manner correspond fairly accurately with the method of biological assay. The Carr-Price colorimeter method is not applicable to the determination of the synthetic preparations of vitamin A.

Although the pure crystalline vitamin A is available, it has no great commercial significance because concentrates of vitamin A may be obtained which are clinically satisfactory. Halibut liver oil is one of the preferred commercial sources of vitamin A. In order to preserve the vitamin A in the fish livers, they are stored in cold under sterile conditions. Otherwise the vitamin A will be readily destroyed.

The method of biological assay of determining the efficacy of a vitamin A preparation as recommended by the U. S. Pharmacopeia is as follows: Young rats whose growth has stopped because of a deficiency of vitamin A are made to gain weight by adding vitamin A. The results obtained are then compared with those produced by the addition of an International Standard preparation of carotene. This standard as supplied by the League of Nations Health Organization is a beta-carotene of which 0.6 microgram is the equivalent of

one International Unit of Vitamin A. The preparation of the carotene employed was made from carrots by the method of Willstätter.

The adaptation to darkness of the eye after being exposed to bright light is also used as a means of determining the minimum amount of vitamin A essential to the organism (Jeans, P. C. and Zentmire, J. *Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency. J. A. M. A.* 102:892, 1934) (Feldman, J. B. *Instrument for Qualitative Study of Dark Adaptation. Arch. Ophthalmol.* 18:821, 1937). This test depends on the fact that night blindness is one of the earliest manifestations of vitamin A deficiency, a point which will be discussed more fully later. Such eyes when examined may be free of any retinal pathology and yet by testing the individual for dark adaptation, early evidence of a deficiency state may be demonstrated. Various methods have been devised for testing the degree of night blindness by the use of adaptometers (Hecht, S. and Mandelbaum, J. *Relation Vitamin A and Dark Adaptation. J. A. M. A.* 112:1910, 1939) (Pett, L. B. *Vitamin A Deficiency. Its Prevalence and Importance as Shown by New Test. J. Lab. Clin. Med.* 25:149, 1939).

Clinically the dark adaptation phenomenon is familiar to us all. Thus on coming from the sunlit outside into a dark room it may take a long time before objects become clear to the field of vision. If one walks into the dimly lighted theatre, from the brightly illuminated street it may take quite some time before one is able to recognize either the audience or any vacant seat. After sometime however, the various objects in the theatre take shape and one may see fairly clearly the faces of the nearby people. This process is described as dark adaptation.

When attempts are made to determine the degree of dark adaptation, various methods of a fairly exact character are employed in order to determine the minimum amount of light which may be visible after definitely stated periods of time.

Another biologic method, the clinical significance of which will be discussed more fully later, depends on the demonstration of pathologic alterations in the appearance of the vaginal smear, the result of a deficiency of vitamin A.

Evans (Evans, H. M. and Bishop, K. S. *On An Invariable and Characteristic Disturbance of Reproductive Function in Animals Reared on a Diet Poor in Fat Soluble Vitamin A. Anat. Rec.* 23:17, 1922) showed that in the female, vitamin A deficiency leads to cornification of the vaginal mucous membrane. This may be shown by the study of a vaginal smear. When however, ample vitamin A is added, the vaginal smear picture becomes normal.

Finally the vitamin A concentration of the blood has been recommended as the most subtle procedure in the determination of the earliest evidence of subclinical deficiency. (Yarbrough, M. E. and Dann, W. J. *Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey. J. Nutrition*, 22:597-607, Dec. 1941) (Bodansky, O., Lewis, J. M. and Haig, C. *The Comparative Value of the Blood*

Plasma Vitamin A Concentration and the Dark Adaptation as a Criterion of Vitamin A Deficiency. Science 94:370-371, Oct. 17, 1941). Diminution in the vitamin A concentration of the blood, may indicate a subclinical state of vitamin A deficiency long before there is any detectable evidence by the dark adaptation method.

THE MODE OF ABSORPTION OF VITAMIN A AND THE FACTORS INVOLVED

There are a number of factors which may produce a vitamin A deficiency state because of their interference with the absorption of the vitamin even when administered in normal amounts.

Bile and the Absorption of Vitamin A

The absorption of vitamin A is disturbed in the presence of jaundice, indicating the importance of bile (Greaves, J. D. and Schmidt, C. L. A. *The Utilization of Carotene by Jaundiced and Phosphorus Treated Vitamin A Deficient Rats. Am. J. Physiol.* 111:502, 1935) (Greaves, J. D. and Schmidt, C. L. A. *On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats. Am. J. Physiol.* 111:492, 1935). In their experiments, Greaves and Schmidt used the vaginal smear technique as a means of determining the absorption of carotene and vitamin A. An internal biliary fistula was established by anastomosing the bile duct to the upper part of the ascending colon, by means of a small silver cannula inserted into the bile duct which was then sewed into the colon.

Those animals that were not operated but were maintained on a vitamin A deficient diet responded within a few days to carotene therapy administered either orally or subcutaneously. The rats subjected to the side-tracking operation failed to respond to the oral administration of carotene, although a therapeutic response resulted from subcutaneous injection.

The evidence indicated that the presence of bile in the small intestine was important for the alimentary absorption of carotene. Vitamin A however, in the form of halibut liver oil was absorbed from the alimentary tract when administered orally even in the absence of bile, although less effectively under such conditions (Greaves, J. D. and Schmidt, *Studies on the Vitamin A Requirements of the Rat. Am. J. Physiol.* 116:456, 1936).

The reason for the disturbance of absorption of vitamin A in the absence of bile in the small intestine is apparently due to the fact that bile is essential for the digestion of fat. In the absence of bile, fat digestion is therefore seriously disturbed. Since vitamin A is fat soluble, its absorption will therefore also be materially affected by those same factors which impede the digestion and absorption of fat.

In this connection, the case of Elschning described in 1899 and referred to in Blegvad's article (Blegvad, O. *Xerophthalmia, Keratomalacia and Xerosis Conjunctivae. Am. J. Ophth.* 7:89, 1924) is of considerable clinical interest. This was the case of a woman fifty-one years of age who was icteric. Physical examination also showed evidence of an enlarged liver and gall bladder and the presence of keratomalacia. Autopsy

revealed a carcinoma of the bile duct with occlusion preventing the entrance of bile into the intestine. The keratomalacia appeared to be the result of the disturbed fat absorption because of the absence of bile in the intestinal tract.

Not only is there a disturbance in the absorption of vitamin A when fat digestion is incomplete because of the lack of bile, but a similar interference may also result from a deficiency of pancreatic lipase, (Clausen, S. W. *Limits of the Anti-Infective Value of Provitamin A (Carotene) J. A. M. A.* 101:1384, 1933) an enzyme also essential for the digestion of fat.

In this connection it is of interest that Breese and McCoord (Breese B. B. Jr. and McCoord, A. B. *Vitamin Absorption in Celiac Disease. J. Pediat.* 15:183, 1939) found deficient absorption of vitamin A in a case of cystic fibrosis of the pancreas.

The Absorption of Carotene as Compared with Vitamin A

The superiority of the active vitamin A as compared with carotenes from the standpoint of absorption was shown by Clausen and McCoord (Clausen, S. W. and McCoord, A. B. *The Carotinoids and Vitamin A of The Blood. J. Pediat.* 13:635, 1938). They showed that when young infants are fed puree of carrot or solutions of carotene in oil, there is a slow rise in the level of plasma carotinoids. The maximum level may not be reached before at least twenty-four hours. When however, large doses of halibut liver oil as a source of vitamin A are administered, examination of the plasma shows a maximum concentration in four hours.

This experimental evidence would indicate the superior value of active vitamin A containing substances, particularly when an attempt is being made to overcome as promptly as possible a sub-clinical or clinical deficiency of this vitamin.

Effect of Short-Circuiting Operations on Vitamin A Absorption

Short circuiting of ingested food interfering seriously with digestion and absorption was the cause of night blindness in the case described by Wilbur and Eusterman (Wilbur, E. L. and Eusterman, G. B. *Nutritional Night Blindness. J. A. M. A.* 102:364, 1934). In their case a gastro-colic fistula had developed secondary to gastric surgery. Most of the ingested food therefore passed directly into the colon. Normal digestion which occurs primarily in the small intestine was therefore seriously interfered with. When the gastro-colic fistula was repaired so that small bowel digestion and absorption again became possible, the night blindness disappeared, owing to the effective utilization of vitamin A.

Vitamin A Absorption and Celiac Disease

The fact that vitamin A is rapidly absorbed from the intestinal tract, showing maximum absorption in the blood in three to five hours is employed as a test of the efficiency of intestinal absorption. According to this test, the vitamin A in the form of halibut liver oil is administered by mouth, and a further study of the vitamin A concentration of the blood is made in three

to five hours. In the presence of coeliac disease, Chesney and McCoord (Chesney, J. and McCoord, A. B. *Vitamin A of Serum Following Administration of Halibut Oil in Normal Children and in Chronic Steatorrhea. Proc. Soc. Exptl. Biol. Med.* 31:887, 1934) observed that the rise of vitamin A in the serum was considerably less than in normal children. With clinical improvement in the condition, there was a marked rise in the vitamin A content of the serum.

Breese and McCoord (Breese, B. B. Jr. and McCoord, A. B. *Vitamin A Absorption in Celiac disease. J. Pediat.* 15:183, 1939) studied the absorption of vitamin A in ten cases of coeliac disease. After a basal blood determination was made, the child suffering from the disease was given fish liver oil in quantity furnishing 7,000 U.S.P. units per kilogram of body weight. Blood determinations were then made 2, 4, 6, 9, 12, and 24 hours later. These tests showed that the child with coeliac disease was unable to absorb vitamin A even after treatment, with the same efficiency as the normal child.

In coeliac disease, the serum and plasma may be colorless because of the diminished amount of carotene. The vitamin A content may also show a marked diminution unaffected by the ingestion of halibut liver oil because of poor absorption from the alimentary tract. Thus a diagnostic procedure in the establishment of the presence of coeliac disease is the demonstration of a failure of a rise in the vitamin A of the plasma after the ingestion of halibut liver oil. Such a finding would lend support to the diagnosis in addition to the presence of increased fat in the stool and a "flat" blood sugar curve.

That absorption of vitamin A is disturbed in the presence of coeliac disease was also shown by Heymann (Heymann, W. *Absorption of Carotene, Am. J. Dis. Child.* 51:273, Feb., 1936).

Fat and Vitamin A Absorption

The relation of fat to vitamin A absorption in different individuals when the same amount of the vitamin is ingested, is indicated by the work of Wilson, Das Gupta and Ahmad (Wilson, H. E. C., Das Gupta, S. M. and Ahmad, Bashir. *Studies on the Absorption of Carotene and Vitamin A in the Human Subject. Indian J. M. Research.* 24:807-811, Jan., 1937). When the diet contained no fat, only fifty percent of the carotene ingested by the human subject was absorbed. When, however, a moderate amount of fat was included in the diet, the absorption of the carotene from the alimentary tract was increased to about ninety percent.

All of these factors indicate the importance of a liberal supply of vitamin A well above that essential for the maintenance of ordinary health, in order to make sure that accidental factors will not interfere with the sufficient utilization of vitamin A, not only for the momentary needs but for ample storage during periods of uncontrollable depletion.

Mineral Oil in Relation to Vitamin A Absorption

That mineral oil may interfere with the absorption of Vitamin A is indicated by the work of Dutcher,

Ely, and Honeywell (Dutcher, R., Ely, J. O., and Honeywell, H. E. *Vitamin Studies XV. Assimilation of Vitamins A and D in Presence of Mineral Oil. Proc. Soc. Exper. Biol. and Med.*, 24:953-955, June, 1927). These authors demonstrated in experiments on rats that mineral oils possess the power of dissolving vitamin A and depleting foods of this vitamin. Thus in one group of rats in which the stored supply of vitamin A had been depleted, a curative dose of butter fat was administered mixed with mineral oil, in the proportion by weight of 2.5 of mineral oil to 1.0 of butter fat. Xerophthalmia developed and death occurred in three cases. On removing the mineral oil, xerophthalmia disappeared and growth recurred.

Similar results on the action of mineral oil in removing fat soluble vitamins from food have been noted in the experimental observations of Burrows and Farr (Burrows, M. T., and Farr, W. K. *The action of Mineral Oil per Os on the Organism. Proc. Soc. Exp. Biol. and Med.*, 24:719-723, April, 1927).

Jeans showed as a result of animal experiments, that when mineral oil is ingested some of the vitamin A is carried away with it in the feces, thus further verifying the work of other observers. (Jeans, P. C. *Vitamin Deficiency in Childhood, Minnesota Med.* 16:688, Nov., 1933). When the amount of vitamin A administered is therefore barely sufficient a deficiency of vitamin A may develop. This however, may be readily overcome by the administration of larger amounts of vitamin A. He described the case of a child with deficient dark adaptation which could not be cured even though fish liver oil was administered for several months. When she was deprived of the mineral oil which she had been taking, her vision promptly became normal.

Vitamin A Absorption and Infections

It has also been shown that the rate of absorption of carotene is diminished in infants as a result of some infections (Heymann, W. *Absorption of Carotene. Am. J. Dis. Child.* 51:273, Feb., 1936). Heymann showed a greatly diminished rate of absorption of carotene in pneumonia, grippe and sepsis. Although healthy children showed excellent absorption when carotene was administered in oil, the infants suffering from the infectious diseases showed a marked decrease of absorption amounting to one-half that of the healthy infant. These infections therefore appeared to interfere with the normal intestinal absorption of carotene.

Vitamin A Absorption and Tuberculosis

Among a group of 197 tuberculous patients, Getz, Hildebrand and Finn (Getz, H. R., Hildebrand, G. B. and Finn, M. *Vitamin A Deficiency In Normal and Tuberculous Persons. As Indicated by the Biophotometer. J. A. M. A.* 112:1308-1311, 1939) found that 53 percent showed evidence of vitamin A deficiency. In the non-tuberculous group only 11 percent showed such vitamin A deficiency. The degree of vitamin A deficiency in the tuberculous individual appeared to parallel the seriousness of the pulmonary involvement. This evidence of vitamin A deficiency was present in spite of the fact that the diet apparently

contained an amount of vitamin A sufficient for individuals in normal health and even though 40 percent of the patients received an additional supply of vitamin A as fish liver oil, not in excess of 30,000 units a day. This indicated that even in the presence of the added vitamin A intake the amount was insufficient for the prevention of a deficiency state. Larger doses of vitamin A therefore appeared to be essential not only in some non-tuberculous individuals but particularly in individuals suffering from tuberculous infection. Doses up to 200,000 units a day might be necessary in refractory cases in order to obtain a normal biophotometric response.

These are therefore added reasons for the addition not only of large amounts of vitamin A during health, but also of making certain that an ample supply is available in chronic disease. When prompt absorption of vitamin A is desired, this may be accomplished more effectively through the administration of natural containing sources of the actual vitamin A such as milk, egg and fish liver oils than through the carotenes.

Vitamin A Absorption and Other Disorders

The absorption of vitamin A may also be disturbed in other disorders. Thus Abels, Gorham, Pack and Rhoads (*Abels, J. C., Gorham, A. T., Pack, G. T.*

and Rhoads, C. P. *Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract I: Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastro-Intestinal Tract, J. Clin. Investigation 20:749-764, Nov., 1941*) (*Abels, J. C., Gorham, A. T., Pack, G. T. and Rhoads, C. P. Metabolic Studies in Patients with Gastro-Intestinal Cancer: III The Hepatic Concentrations of Vitamin A, Proc. Soc. Exper. Biol. and Med. 48:488-492, Nov., 1941*) found a diminution in the plasma level of vitamin A in 86 percent of patients suffering from cancer of the gastro-intestinal tract.

The low plasma level of vitamin A in such patients was shown not to be due to an inability of the liver to store vitamin A.

Page and Bercovitz (*Page, R. C. and Bercovitz, Z. The Absorption of Vitamin A in Chronic Ulcerative Colitis. Amer. Jour. Digestive Diseases, 10:174, May, 1943*) studied twenty-five patients with chronic ulcerative colitis. Following the oral administration of 100,000 U.S.P. units of vitamin A in the form of fish oil concentrates, they found a lower plasma vitamin A level than in normal controls. The disturbance may be best explained on the basis of disturbed absorption associated with diarrhoea.

(To be continued in May 1944 Issue)

Autonomic Pharmacology and Therapeutics of The Gastro-Intestinal Tract*

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THE exigencies of human life require that individuals react properly to their external environment, and also that the cells composing the organs of the individual act harmoniously and do not thwart one another (i.e. react properly to the internal environment). The cerebrospinal nervous system insures the optimal exterior conditions for life, and enables the individual through his sense organs, skeletal system and voluntary muscles to change his external environment. The effect of the autonomic nervous system is to adjust the internal functions of the body, such as blood circulation, respiration, digestion and excretion so that they are coordinated for the benefit of the body cells. The metabolic operations of the body incident to the demands of everyday life cause certain changes in the internal environment of the body, i.e., changes in pH, body temperature and osmotic pressure of the blood, and therefore require adjustments by the organs of the body. These adjustments are made by the autonomic nervous system.

There is one fundamental anatomical difference between the cerebrospinal or "voluntary" nervous system and autonomic or "involuntary" nervous system. The fibers of the autonomic nervous system do not run directly to their effector organs, but are interrupted at a break or synapse. Many of these synapses

combine to form a ganglion. The post-ganglionic fibers come from these ganglia and then directly innervate the effector organs, i.e., stomach or other organs.

However, the central nervous system and the autonomic nervous system can not be so definitely and completely separated. For example, it is well known that most autonomic functions are under central nervous system influence. Pleasurable emotions promote visceral functions, while unpleasant emotions suppress them. It has also been shown that there are groups of cells in the hypothalamus, medulla, and midbrain that control autonomic function. These are the higher vegetative centers. Some of the functions controlled by these centers are the contraction of urinary bladder uterus, the regulation of body temperature, the elimination of water and other functions less definitely studied.

Autonomic activity, as a rule, is concerned with those functions which are carried beneath the level of consciousness. Therefore, cardiac, gastro-intestinal, endocrinological and other activities are dominated by this system. Most of the organs governed by autonomic nervous system are innervated by both the sympathetic and parasympathetic branches of this system. In general these divisions have opposing and counterbalancing actions, thus maintaining normal tone in these innervated organs. However, one division is not always an inhibitor or accelerator, for instance, para-

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sympathetic stimulation slows the heart and sympathetic stimulation accelerates it; while on the other hand, parasympathetic stimulation activates the intestinal tract and sympathetic stimulation slows it. Over-activity or under-activity of either division upsets the delicate balance and causes disturbed physiological function.

Sympathetic activity plays an important role in emergencies. The results are widespread, and (along with the activity of the central nervous system) takes the animal out of the harmful external environment. Parasympathetic activity is more localized and concerned with conservative and restorative processes (in the internal environment.) Sympathetic activity is related to catabolism or breaking down, while parasympathetic activity is related to anabolism or building up. The varying effect on different organs of even one of these systems is so complex, that we might expect complete chaos from its stimulation. However, when we think of the purposefulness of the reaction to that organ, we see how the effects in the different organs integrate with one another. For example stimulation of the sympathetic decreases the heart rate, causes a dilation of the coronary arteries, increases the blood pressure, dilates the bronchi, inhibits the gastro-intestinal tract and liberates glucose into the blood. These activities are all directed to one purpose, since they prepare the body for an emergency.

Stimulation of the parasympathetic system causes a restitution of the organism to a resting state when the stress is over. Sleep is induced, blood pressure and the heart rate is reduced, muscle tone is diminished, and the elevated blood sugar is depressed by the action of insulin.

The sympathetic stimulants are adrenalin, benzedrine, and ephedrine. The sympathetic inhibitors are ergotamine (gynergen) and ergotoxin. The parasympathetic stimulants are acetylcholine and its derivatives. Pilocarpine, physostigmine, and prostigmine have similar actions, although the mechanism is different. The parasympathetic inhibitor is atropine. The mode of action of these substances can be easily understood from the diagram on the next page.

In view of the importance of the autonomic nervous system in visceral functions, it can easily be seen how important imbalance is to gastro-intestinal dysfunction. The general rule can be given, that in the intestinal tract the parasympathetic system is motor, and the sympathetic system is inhibitory. However, the sphincters are considered to be innervated in opposite fashion.

Some of the conditions of the gastro-intestinal tract that involve the autonomic nervous system will now be discussed.

Cardiospasm: Cardiospasm or achalasia of the esophagus is a very interesting condition. It is considered to be due to overactivity of the sympathetic system. This is proven by the fact that vagal section results in cardiospasm. It can be seen how futile it would be to give atropine, as is usually given for this condition. Atropine theoretically would make the spasm worse. Actually it does no good. Prostigmine has recently been given with success by the Michael Reese Hospital group. (1)

Physiology of Gastric Secretion (2): There are at least two phases of gastric secretion. One is the nervous or vagus phase, in which the thought, sight, and odor of food produces impulses over the vagus nerve, thereby causing secretion of hydrochloric acid and gastric enzymes. This phase is abolished by vagal section and therefore atropine. There is also a chemical phase, in which a hormone called gastrin acts directly on the fundus cells (of the stomach) without nervous intervention. Histamine acts in this way. In fact, it has recently been shown that gastrin and histamine may be identical. There is also an inhibitory factor present in the duodenum and jejunum called enterogastrone, which is excreted in the urine. This substance has recently been given by a research group in an effort to accelerate the healing of gastric ulcers.(3) In partial gastrectomy, for gastric ulcer the removal of the antrum abolishes the second or chemical phase of secretion of acid. The remainder of the secretion is neutralized by intestinal regurgitation. In some patients with a very high pre-operative secretion of acid, vagal section plus partial gastrectomy is sometimes done to insure achlorhydria and therefore prevent recurrence of the ulcer (4).

Gastric and Duodenal Ulcer: The association of gastric and duodenal ulcer with parasympatheticotonia has been shown by many writers, especially Cushing (5). He showed that stimuli emanating from the central autonomic centers of the mid-brain (lesions of tuber cinereum) brought about gastric erosions, probably by way of the parasympathetic system. Recently also, gastric ulcers were produced by histamine (a parasympathetic stimulant) by way of injection of a histamine-beeswax mixture into guinea pigs (6).

In gastric and duodenal ulcer, hypersecretion of acid is an almost constant concomitant finding, which is indirect evidence of a parasympathetic preponderance.

Control of Pyloric Sphincter (7): The control of the pyloric sphincter is considered to be somewhat as follows:

Fluid gastric contents, plus increased intragastric pressure and decreased intraduodenal pressure opens the pylorus. The presence of acid in the duodenum closes the pylorus. If the rule mentioned earlier in this paper holds, the sympathetic system should influence the pylorus by closing it. Actually it appears as if the vagus nerve is motor to the pylorus, because atropine reduces the tension and relaxes it. Its use is well known in pyloric spasm and the hypertrophic pylorus of infants.

Division of the extrinsic nerves do not profoundly modify the mobility of the stomach or intestines (8). Section of the sympathetic or parasympathetic supply produces temporary changes only. Many activities of the gastro-intestinal tract involve only the enteric nervous systems (Meissner's and Auerbach's. Plexus in the submucosa of the intestinal tract). Certain types of motility, as for example, rhythmic contractions are actually myogenic, but these are subject to continuous restraining influences exerted by the enteric nervous plexus. Over these effects reign the extrinsic sympathetic and parasympathetic nerves.

A great deal of pharmacological research has been done to obviate the disadvantages which limit the usefulness of some of the autonomic stimulants and depressants. One of the most useful of these substances is prostigmine, a synthetic physostigmine-like preparation, which stimulates the parasympathetic system without causing miosis or cardio-respiratory depression.

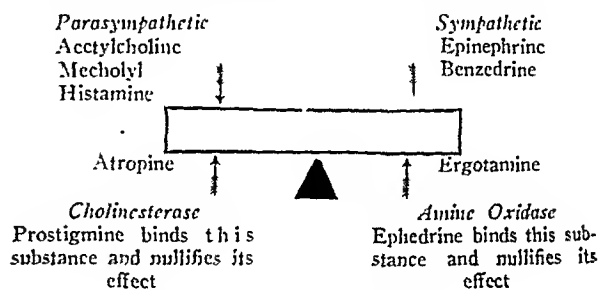
Paralytic Ileus: One of the most important functional abnormalities that calls for a parasympathetic stimulant is paralytic ileus. The vagus-potentiating action of prostigmine is here so definite and obvious that it has been called a vagomimetic drug. Vagus impulses counteract the inhibitory influences of the sympathetic system and so reinforce the strength of the gastro-intestinal muscles. Post-operative distention is the common form of paralytic ileus that we see, and here the results are no less than brilliant (9). Prostigmine methylsulphate, 1/2000, 2 c.c. is given intra-muscularly every four hours for three doses. Distention disappears rapidly. Catheterization is also obviated in many cases by virtue of the prostigmine effect on the sacral autonomic supply of the urinary bladder (10). Prostigmine is also used to dispel shadow producing gas as a preliminary to abdominal roentgen examination (11).

Spastic Constipation: Spastic constipation is considered by some to be a pure parasympatheticotonic condition. It can be seen how futile the cathartics alone would be in its treatment. The treatment should also include an atropine derivative to overcome the spasm of the colon.

Megacolon: Megacolon is an interesting condition considered to be due to an imbalance of the two opposing nervous supplies of the large bowel and anal sphincter, with a preponderant sympathetic activity (12). The result is an extremely dilated proximal lower colon, because of the inhibition of its tone, and the relative obstruction of the distal part. This is apparently demonstrated by the fact that spinal anesthesia immediately increases the activity of the colon. Spinal anesthesia reduces or nullifies sympathetic activity on the gastro-intestinal tract. (13). Sympathectomy also increases the activity of the colon in this disease. The findings after both sympathectomy and spinal anesthesia is a bowel reduced to about half the former size. Prostigmine also helps these patients.

There is some thought that most of the pathology of the gastro-intestinal tract may be largely initiated by psychogenic influences (14). Since the vegetative

nervous system forms the point of contact between the psyche and the soma, it is intimately involved also in psychogenic disturbances. Anxiety, for example, might cause an outpouring of acetylcholine. This causes increased peristalsis or spasm of the gastro-intestinal tract, increased secretion and according to recent work, a local ischemia. Acetylcholine has been shown to have two actions, a muscarine-like action which is long lasting and can be blocked by atropine, and a nicotine-like action which is rapid, but brief. If these influences can be made to continue long enough there is bound to be a lowering of resistance of the gastro-intestinal tract which prepares the way to secondary invasion of bacteria, their toxins or other toxic substances. Perhaps this lowering of resistance may predispose portions of the gastro-intestinal tract to the effects of certain deficiency states. It is interesting to speculate what effect this phenomenon has in the production of a disease like ulcerative colitis or peptic ulcer.



Some Autonomic Drugs and Dosage

A. Parasympathetic Stimulants:

Prostigmine

Oral—15 mgm. tablet—repeat as necessary
Subcutaneous—1.0-2.0 cc (1/200) every 4 hrs.

Physostigmine

Oral—1/30 grain tablet—repeat as necessary
Subcutaneous—1/20-1/60 grain

B. Parasympathetic Depressants:

Atropine Sulfate—Oral or Parenteral—1/10-1/60 grain
Belladonna (Tincture)—Oral—10-15 Minims three times daily

Novatropine—Oral—2.5 mgm. tablets three times daily
Syntropan—Oral—50. mgm. tablets three times daily

C. Sympathetic Stimulants:

Epinephrine—Subcutaneous—2.5 cc (3-8 Minims)

Ephedrine Sulfate—Oral—¼-¾ grain three times daily
Topical ¼%-3% as drops for nose

Benzedrine Sulfate—Oral—5-10 mgm. three times daily

D. Sympathetic Depressants:

Ergotamine Tartarate (Gynergen)—Oral—1 mgm.
(1/60 gr.) three times daily
Subcutaneous—¼-1 cc (1 mgm. per cc)

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Peptic Ulcer—Suggesting Malnutrition as The Etiology

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THIS thesis is presented without details and without references, since the aim is not to prove anything but to suggest to research men and clinicians—for consideration and criticism, an approach to the study of the etiology, and especially to the study of a method for effective prophylactic treatment of peptic ulcer.

The present accepted system for medical treatment of peptic ulcer is reasonably satisfactory, in that the ulcer can frequently be healed by strict medical treatment in a few months' time. It is the long-time threat of recurrence, and the tedious palliative and preventive care for years which makes life miserable, with surgery as the final resort in many cases. Drastic surgical measures may prevent recurrence of the ulcer without alleviating associated symptoms, or removing the underlying cause in patients unfortunately so affected. The object here then, is to suggest for criticism a means of ridding these patients of their ulcer diathesis.

If it is suggested that the approach herein outlined is not rational, it is counter-proposed that if the treatment is beneficial to some patients and harmful to none, it may safely and profitably be applied before science reveals the rationale.

Present teaching is that the patient frequently is of a nervous disposition and following the healing of the ulcer must live moderately, avoid excitement and worry, delegate responsibility whenever possible, follow modified ulcer dietary instructions, drink alcoholic beverages and smoke tobacco in great moderation—if at all. He must see his physician from time to time, and at the first sign of recurrence of ulcer symptoms begin again for an indefinite period the strict ulcer regimen.

The theory presented is that the cause of peptic ulcer is to be found in sluggish inefficient liver action. Recent investigations indicate that the highly specialized liver cells may undergo varying degrees of deterioration when a diet deficient in essential nutrients is taken, especially over a prolonged period of time. If the dietary deficiencies are not supplied, in time the degenerative processes become increasingly progressive, and finally demonstrable microscopic and gross organic pathological changes occur in the liver parenchyma, possibly through various precirrhotic changes to fully developed liver cirrhosis.

Such diets may be low in proteins, fats, carbohydrates, vitamins, minerals or calories. Recent research suggests that they are frequently low in certain essential amino-acids and in members of the vitamin B. complex.

It is pointed out here that men who do research on the liver have apparently not found peptic ulcer nor allergy (which is mentioned below) to be associated with liver cirrhosis. However, it is suggested that in

these cases of malnutrition (peptic ulcer and allergy) there may early develop a sluggish excretory function and diminished metabolic liver activity, with incomplete preparation here of even available nutrients, partially due to interlocking action, for the further metabolic changes which occur in the tissues. This leads to faulty tissue metabolism, and in this instance gives rise to the areas of so-called "lowered resistance" in the gastric and duodenal mucosa, whereby an irritant of endogenous origin—the HCl of the gastric juice, acts chemically on this area of mucosa in such a manner as to cause tissue destruction and ulcer formation.

Again this idea may account for the central nervous theory of the cause of peptic ulcer as well. It has been shown at various times that organic lesions of the brain are at times associated with peptic ulcer; also it has been demonstrated that increased HCl secretion in the gastric juice and increased gastric mobility may result—and commonly do result, from nervous excitation. It is here suggested that where peptic ulcers occur without symptoms or signs of demonstrable brain pathology, the central nervous stimulation causing increased HCl secretion and increased muscular contractions of the stomach as occurs in these cases during spasms of ulcer pain, may be caused by the same faulty tissue metabolism producing irritable local areas of lowered resistance in the brain substance, as causes them in the gastro-intestinal mucosa.

Since some peptic ulcer cases and some allergy cases have been found to benefit by similar treatment, mention is made of allergy and a relationship suggested. The process of peptic ulcer development then may be considered comparable to the production of allergic phenomena, in that here there is an area of lowered resistance on which an external irritant, the HCl of the gastric juice, acts to cause tissue destruction. In allergy there appears to be areas of lowered resistance in the tissues on which an irritant of endogenous or exogenous origin acts, resulting in the sudden alarming reactions of allergy as occurs in asthma, hay fever, eczema, etc. In this process histamine is conceded a leading role. When the cause of local ulcer formation in peptic ulcer cases and the cause of local allergic reactions are revealed they may be found to have a common basis. Also other sudden reactions in the body in which the cause is now obscure, as in some cases of sudden heart failure, and even in some so-named menopausal symptoms.

Sufficient experimental work has been done to indicate that some recurring allergic manifestations vanish when the patient is prescribed a balanced diet. In such cases, especially where there have been nutritional deficiencies over a prolonged period of time, good results are most consistently obtained, and obtained earlier when in addition to a balanced diet with sufficient

bulk, proteins, carbohydrates, fats, vitamins, minerals and fluids, vitamin concentrates in generous dosages, and an iron salt are also prescribed.

The vitamins thus supplied here as a rule include vitamins A, D, C. and the B. complex. Liver extract for oral administration is always prescribed, and in some cases for intramuscular administration as well.

In cases of malnutrition of any order or degree, in the absence of contra-indications, iron is given routinely, even when estimation of the haemoglobin percentage in the blood shows a normal reading.

It was found in practice that a large percentage of cases of malnutrition did not respond fully until in addition to a balanced diet with vitamin concentrates and iron, a cholagogue in effective dosages was prescribed. On the other hand, as expected, cholagogue therapy alone has not been found effective.

Where there is marked indication for choloretic therapy, as a rule a moderately low fat, moderately high carbohydrate diet and a low meat diet is prescribed for a time.

According to Beckman, the cholagogue of choice for medicinal use is bile salts. In addition to their action as a cholagogue they are considered to have a choloretic and a cholepoietic effect as well. The fact that effective dosage causes a flow of bile from the common duct whether the gall bladder has been removed or not proves the choloretic action. In most cases treated here at present a pharmaceutical preparation of desiccated whole bile is used.

Of a variety of symptoms indicating the use of a cholagogue in this practise, the two most constant are a sensation of fullness and distension or even pain in the upper abdomen frequently, and fatigue. The upper abdominal discomfort occurs most commonly following meals, especially when certain foods as fats, cabbage, fried foods, etc. are served. This symptom occurs typically in cases of cholecystitis where gallstones may or may not be present, and frequently is not relieved by cholecystectomy until a choloretic is prescribed.

Incidentally, it is suggested that malnutrition as it applies to the liver and biliary tract may yet be found to be the chief cause of cholecystitis.

The other most frequently noted symptom is fatigue, especially sudden attacks of fatigue, which cannot be accounted for by anything in the history of any finding in the physical or laboratory examination. These two symptoms are found to be troublesome in most if not all the cases of allergy seen and investigated. Other recurrent symptoms which are sometimes relieved by cholagogue and balanced diet therapy are headaches, general and regional, and sore eyes, when no organic cause is found on examination, and many vague abdominal pains of inorganic origin. Also hyper-excitability and restlessness are relieved in really many of the cases so treated, and varying degrees of from mild to moderate mental depression. A number of these symptoms are usually associated in peptic ulcer and allergy cases.

Here is quoted a case of eczema illustrating that some symptoms and signs of allergy are even accentuated with the above dietary treatment including vita-

min concentrates until a cholagogue is prescribed as well. This patient, a woman of 34 years, when first seen in October 1941 had for several years very itchy erythematous and oedematous areas of skin around the eyes and ears. These were more troublesome at times than others. For years there had been an unnatural fatigue a good deal of the time and an increasing mental depression. She did not enjoy meeting people as she seldom felt like joining in conversation. There had frequently been a slight sensation of fullness in the upper abdomen following meals. She had seen a number of doctors, one of whom prescribed desiccated thyroid gr. 1 daily six months previous to this office visit. It had helped to relieve the fatigue a little. P.X. was negative except for the eczema. A balanced generous diet to include the above named concentrates was prescribed. In one week the patient was feeling considerably better, but the eczema was worse than it had ever been and the eyes were affected. There was considerable injection of the conjunctivae accompanied by lacrymation and photophobia. A cholagogue in effective dosages was now prescribed in addition to previously mentioned treatment. In a few days the eczema was gone. This patient was seen over a year later, she was feeling much better. The unnatural fatigue and mental depression had not recurred. There had been no recurrence of the eczema.

It is recognized that patients with peptic ulcer may present a variety of symptoms. Some of these simulate those of cholecystitis or liver dysfunction. When however, a diagnosis of gastric or duodenal ulcer is definitely made, by review of symptoms, X-ray findings and possible gastroscopy confirmation, ulcer treatment is instituted, and the gall bladder symptoms are ignored. Under the beneficial influence of rest in bed, freedom from worry and responsibility, strict ulcer diet, etc., all the symptoms gradually subside. During the long course of treatment the patient feels himself to be temporarily more or less useless, and often is not restored to full productive capacity to work even when the ulcer is healed, but—as has been mentioned, must continue a tedious modified treatment for years.

Following are brief reviews of four cases of duodenal ulcer, illustrating the effect of treatment when the accepted strict ulcer regimen is fortified by prescription of potent pharmaceutical preparations of vitamins and iron, and effective cholagogue therapy. A full-balanced diet is prescribed as early as feasible. The vitamin preparations, liver extract and iron are given for three week periods several times a year. Some patients seem to require cholagogue therapy once or twice a week for years or oftener; some require it for a few weeks only, and some, possibly where little liver damage has occurred, do not need it at all.

Case 1—Mr. C. B.

Age 40 when first seen in November 1938.

Ten years previously a duodenal ulcer had been diagnosed by his physician on the history, symptoms, physical findings and X-ray. There had been no complications, but the patient was very ill and lost considerable weight. Strict sippy diet and alkaline powders were taken regularly for several months and olive

oil—1½ oz. in orange juice, 4 to 6 oz. t.i.d.a.c. A smooth diet had been taken a good deal of the time ever since, and alkaline therapy was still taken at times to relieve a burning pain in the epigastric region of the abdomen.

For two or three years preceding this consultation there had been an intractable eczema in several areas of the skin of the body; recently eczema had developed over the face and ears. During these years fatigue was increasingly troublesome and at times amounted to exhaustion. Constipation was becoming increasingly marked and there was a heavy, loggy sensation in the whole abdomen frequently. There was no sensation of fulness, nor tenderness on palpation in the right upper quadrant of the abdomen.

Physical examination was chiefly negative except that the patient was under-weight and appeared very tired and "nervous". Laboratory findings, gastric analysis, blood and urine examinations were negative.

The patient was prescribed a balanced diet, chologogue therapy, vitamin concentrates, an iron salt and liver extract per ora daily and intramuscularly every two or three weeks.

June 30, 1943—As long as these medications are continued periodically this patient feels well. There has been no epigastric pains for years, nor eczema.

Case 2—Mr. T. G.

Age 35 when first seen in February 1940.

For some time there had been symptoms suggestive of peptic ulcer. The pains in the epigastric region were becoming more troublesome. Xray examination at this time showed evidence of a duodenal ulcer.

Treatment prescribed included rest in bed for a few weeks, a strict ulcer diet, alkaline powders, olive oil 1½ oz. in 6 oz. orange juice t.i.d.a.c., an iron salt and the usual vitamin concentrates. The patient was kept on a smooth nutritious diet for three weeks after all pain had disappeared. He adhered to treatment for a few weeks, then omitted the pharmaceutical preparations.

On April 10, 1943, this patient reported he had now been a bed patient for over two weeks. The ulcer pain had recurred severely two or three weeks ago, after he had been entirely free from it for a year and a half. He had seen a doctor who advised him to again go on the strict ulcer regimen.

At the time of this consultation the patient was exceedingly uncomfortable. In addition to frequent spasm of ulcer pain, there was a fairly marked sensation of fulness and discomfort in the upper abdomen, which had as yet not been relieved by the prescribed treatment. There was a considerable degree of restlessness and insomnia was troublesome.

A chologogue in effective dosages, to be taken daily for awhile, was prescribed; also the pharmaceutical preparations of vitamins and iron as before.

In a day or two the feeling of abdominal distension was relieved. In a few days the ulcer pains disappeared completely. In ten days—against advice, the alkaline powders were discontinued, a full diet resumed and the patient went back to work.

June 30, 1943. The patient is very well. If the chologogue and dietary treatment are not continued consistently it is anticipated there will be further relapses. If treatment had not been begun early in the latest relapse it is entirely likely that tissue destruction in the affected area of mucosa would have progressed further, requiring months of special care to ensure complete healing.

Case 3—Mrs. M. P.

Age 26 when first seen in office April 19, 1941.

This patient had had the gall bladder and appendix removed several years previously. For many months now there had been frequently a feeling of fulness in the upper abdomen after meals; also a vague burning pain in the epigastric region. Cabbage and fats were avoided in the diet. In November 1940 her physician had given a diagnosis of peptic ulcer, although no Xray had been taken. At that time she had been prescribed a smooth diet and alkaline medication.

The patient's chief complaint at this office visit was fatigue. She had been "lacking in pep" for a long time. A complete check was refused at this time, only a hurried physical examination was done. The patient was a little overweight; B.P. 100/64, pulse rate 66, otherwise the examination was negative. A B.M.R. was not done, an Xray was not taken, gastric analysis was not done.

Treatment prescribed included a smooth nutritious diet with vitamin concentrates and iron, alkaline medication, dessicated thyroid gr. 1 daily and a chologogue in effective dosages.

The patient was again seen June 10, 1941. There had been no abdominal pain since a few days following the last visit two months previously. For several months at this time there was no pain and the patient felt generally much better. Treatment was not followed after the first few weeks.

On February 10, 1942, Mrs. P. reported that for several days she had not been feeling well. There was fairly severe recurring pains in the epigastric region; the appetite was poor, with occasional emesis. There was no definite sensation of pain or fulness in the right upper quadrant of the abdomen.

An Xray examination now confirmed a diagnosis of duodenal ulcer; also there was abnormal gastric retention following a test meal. Advice was that strict medical treatment for ulcer be prescribed for a few weeks, then if indicated surgery could be contemplated. However, the symptoms were again completely relieved by essentially the same treatment which had been followed in June 1941 as described.

May 1943—At this time the patient reported she had been free from abdominal pain for well over a year and feels very well.

Case 4—Mr. H. J.

Age 28 at first office visit January 30, 1943.

At this time the patient had frequent spasms of ulcer pains and complained of feeling tired most of the time.

There had never been a sensation of fullness and discomfort in the right upper quadrant of the abdomen. He had been discharged from the army in December 1942 following a hemorrhage from duodenal ulcer. Following the hemorrhage he had been given treatment for the resulting anaemia. On return to work his physician advised him that he could take any diet, but to continue to take alkaline medication and milk regularly between meals and whenever necessary for

the relief of the ulcer pain, and to avoid citrus fruit juices. No other medications were prescribed.

P. X.—The patient appeared young and healthy except for a fairly marked pallor.

Treatment prescribed included all the things prescribed in other cases in this series except the choline.

April 10, 1943.—There has been no abdominal pain for weeks. The patient looks and feels very well.

Study of One Hundred and Twenty-Seven Cases of Arthritis (With Notes on Gastro-Intestinal Features)

By

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ALTHOUGH much has been done during the past decade to advance our knowledge and increase our powers of control over that group of pathologic conditions usually designated as arthritis, the entire subject is still more or less obscure. It is not with the idea of making a new and startling exposition, but rather of adding to the mass of data already accumulated, and thereby strengthening the foundation upon which we may some day hope to erect a firm superstructure of comprehension and treatment, that I am presenting this series of cases coming under my personal observation. To this end the marshalling of even what appears to be trivial facts may not be without value, though to avoid the tedium of considering a mass of detail I am—so far as possible—presenting it in tabular form.

Personal Histories

Table 1

	No. of Cases	Married	Single	Widowed
Male	29	20	6	3
Female	98	48	25	25
Total	127	68	31	28

Comment on Table 1: Females greatly predominate, the ratio being 3.4 to 1. In regard to the marital state, the ratio between the married and widowed of both sexes to the single is 3 to 1; of married and widowed women to single women a trifle less than three to one; of married and widowed men to single men almost 4 to 1. Other comparisons can be readily made.

Comment on Table 2: This table sets forth the age at which the patient was first affected by arthritis, and the number of years the disease had been present. The cases are grouped into ten year periods, showing the number of affected in each decade of life, and the sex incidence. In the last column the age at onset is contrasted with the age at which consultation was first made shown in the second column.

Table 3

Age	1-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
No. of Cases	6	3	8	14	27	51	21	2

Comment on Table 3: Here we have the figures already shown in Table 2, indicating the age decades in which patients came for consultation, enabling us to gain some idea of the time of life in which arthritis is

most prevalent. There is a steady increase with each decade up to the sixth; thereafter there is a decline at first equaling the corresponding rise in the fifth decade, but then becoming much more rapid as the more advanced ages are reached. In my opinion this decline in the number of elderly and aged patients coming for consultation is not because arthritis is less prevalent at these ages, but because the old look upon joint infirmities as inevitable at this time of life, and make no effort to seek relief. There is urgent need for public education on this particular point. Efficient examination and treatment of these elderly people would undoubtedly prolong life and make the declining years immeasurably more comfortable and useful. No importance should be attached to the fact that my list contains no patients at certain age periods—21 to 25 for example. In a larger series these ages would undoubtedly all be represented. Of the earliest years 1-10 these omissions have more significance. My experience

Table 4

Duration	Female	Male	Total Male and Female	Age at Onset
1-2	2	2	4	
3-4	6	1	7	
5-6	1	2	3	
7-8	10	2	12	
9-10	8	4	12	
11-12	5	3	8	
13-14	7	1	8	54
15-16	3	1	4	
17-18	4	2	6	
19-20	2	0	2	
21-22	1	0	1	
23-24	21	6	27	41
25-26	3	0	3	
27-28	1	0	1	
29-30	7	1	8	12
31-32	1	0	1	
33-34	2	1	3	
35-36	5	1	6	10
37-38	1	0	1	
39-40	1	0	1	
41-42	1	0	1	
43-44	1	0	1	
45-46	1	0	1	
47-48	1	0	1	
49-50	1	0	1	
51-52	1	0	1	
53-54	1	0	1	
55-56	1	0	1	
57-58	1	0	1	
59-60	1	0	1	
61-62	1	0	1	
63-64	1	0	1	
65-66	1	0	1	
67-68	1	0	1	
69-70	1	0	1	
71-72	1	0	1	
73-74	1	0	1	
75-76	1	0	1	
77-78	1	0	1	
79-80	1	0	1	
81-82	1	0	1	
83-84	1	0	1	
85-86	1	0	1	
87-88	1	0	1	
89-90	1	0	1	
91-92	1	0	1	
93-94	1	0	1	
95-96	1	0	1	
97-98	1	0	1	
99-100	1	0	1	
101-102	1	0	1	
103-104	1	0	1	
105-106	1	0	1	
107-108	1	0	1	
109-110	1	0	1	
111-112	1	0	1	
113-114	1	0	1	
115-116	1	0	1	
117-118	1	0	1	
119-120	1	0	1	
121-122	1	0	1	
123-124	1	0	1	
125-126	1	0	1	
127-128	1	0	1	
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135-136	1	0	1	
137-138	1	0	1	
139-140	1	0	1	
141-142	1	0	1	
143-144	1	0	1	
145-146	1	0	1	
147-148	1	0	1	
149-150	1	0	1	
151-152	1	0	1	
153-154	1	0	1	
155-156	1	0	1	
157-158	1	0	1	
159-160	1	0	1	
161-162	1	0	1	
163-164	1	0	1	
165-166	1	0	1	
167-168	1	0	1	
169-170	1	0	1	
171-172	1	0	1	
173-174	1	0	1	
175-176	1	0	1	
177-178	1	0	1	
179-180	1	0	1	
181-182	1	0	1	
183-184	1	0	1	
185-186	1	0	1	
187-188	1	0	1	
189-190	1	0	1	
191-192	1	0	1	
193-194	1	0	1	
195-196	1	0	1	
197-198	1	0	1	
199-200	1	0	1	
201-202	1	0	1	
203-204	1	0	1	
205-206	1	0	1	
207-208	1	0	1	
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211-212	1	0	1	
213-214	1	0	1	
215-216	1	0	1	
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223-224	1	0	1	
225-226	1	0	1	
227-228	1	0	1	
229-230	1	0	1	
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233-234	1	0	1	
235-236	1	0	1	
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249-250	1	0	1	
251-252	1	0	1	
253-254	1	0	1	
255-256	1	0	1	
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261-262	1	0	1	
263-264	1	0	1	
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267-268	1	0	1	
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321-322	1	0	1	
323-324	1	0	1	
325-326	1	0	1	
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341-342	1	0	1	
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345-346	1	0	1	
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349-350	1	0	1	
351-352	1	0	1	
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361-362	1	0	1	
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621-622	1	0	1	
623-624	1	0	1	
625-626	1	0	1	
627-628	1	0	1	
629-630	1	0	1	
631-632	1	0	1	
633-634	1	0	1	
635-636	1	0	1	
637-638	1	0	1	
639-640	1	0	1	
641-642	1	0	1	
643-644	1	0	1	
645-646	1	0	1	
647-648	1	0	1	
649-650	1	0	1	
651-652	1	0	1	
653-654	1	0	1	
655-				

Table 2

No. Cases at age Age Cons. period	Total 10 yr. F M	Total F M	No. Years Arthritis	Ages at onset
16	0	0	0	0
17	1	0	4	13
18	0	0	0	0
19	1	0	2	17
20	1	3	0	18
26	2	2	3, 4	23, 22
27	1	0	0	21
28	1	1	8	20
29	1	0	5	24
30	3	8	2, 10	28, 20
31	1	1	3	28
32	1	1	2	30
33	2	2	7, 1	32, 26
34	1	1	12	22
35	0	0	0	0
36	1	1	10	26
37	1	1	10	27
38	1	1	2	36
39	1	1	10	29
40	5	14	2, 10, 3	38, 30, 37
41	1	0	3	38½, 30
42	2	2	10, 4	38
43	4	4	1½, 1½, 25, 2	32, 38
44	3	3	9, 2, 30	42½, 41½, 18, 41
45	4	4	2, ½, 30, 3	35, 42, 14
46	1	0	0	43, 44½, 15, 42
47	4	4	7, 15, 40, 10	0
48	1	1	10	40, 32, 7, 37
49	2	1	2	38
50	7	29	4, 10, 20, 1, 17, 3, 18	47
51	3	3	10, 10, 5	46, 40, 30, 49, 33, 47, 32
52	4	3	4, 5, 45	41, 41, 46
53	4	4	1, 1, 12, 15	48, 47, 7
54	5	3	1, 10, 22	52, 52, 41, 38
55	9	6	15, 2, 10, 10, 3, 30	53, 44, 32
56	6	6	10, 5, 7, 3, 10, 8	25, 40, 52, 53, 45, 45
57	3	2	7, 20	46, 51, 49, 53, 46, 48
58	7	3	10, 4, 20	50, 37
59	7	5	5, 10, 27, 5, 10	48, 54, 35
60	2	50	6, 30	54, 49, 32, 54, 49
61	0	0	0	54, 30
62	2	0	0	0
63	4	3	6, 15, 6	0
64	2	2	15, 5	52, 55
65	0	0	0	56
66	2	1	10	49, 59
67	5	5	5, 15, 1, 20, 10	0
68	4	4	18, 20, 15, 13	56
69	1	1	12	62, 52, 66, 57, 47
70	1	21	3	50, 48, 53, 55
71	0	0	0	57
72	0	0	0	67
73	1	0	0	0
74	0	0	0	0
75	0	0	0	71
76	1	2	29	0
127	127	98	27	98
			29	

appears to coincide closely with that of other observers that though arthritis *may* afflict persons of any age, it is rare before adolescence. Of my two patients in the eighth decade, one consulted me because of the joint condition, which was his only complaint. The complaint of the other was asthma, with which arthritis proved to be associated.

Comment on Table 4: In this table we have the length of time arthritis had been present in the different cases, divided into five year periods. The shortest period was six months; the longest 45 years. As might be expected, the period of from six months to five years shows the greatest number coming for consultation; in these two first five year periods we find 94 cases.

In a second five-year period there are 27 cases—that is 27 patients had suffered from arthritis for 10 years before seeking relief by systematic study. In all periods it will be noted that females had suffered for relatively longer time than males; indeed in three of the five-year periods—the fifth, seventh and eighth—no males appear. This is in keeping with the preponderance of females throughout the series. Twenty-nine years' duration is the only time-period not represented by a female. It is noticeable that after an individual had suffered for ten years or more he is far less likely to come for relief. I believe this to be because many have tried various remedies without benefit, and after the lapse of ten years become so discouraged that they

follow the admonition of Hamlet by deciding to endure the evils that they have, without further striving for relief.

Comment on Table 5: In this table I have endeavored to demonstrate the varying ages at which arthritis first attacks its victims. The earliest age reported by any of my patients was seven years; two females had first manifested the condition at that age. One man had first experienced arthritis at the age of 71. It will be noted that the fourth decade of life (31-40) has several years unrepresented. The greatest incidence is in the fifth decade where 38 cases appear; the sixth decade is the next with 31 cases; the fourth decade third with 24 cases. Thus we see that the incidence of arthritis rises with advancing age until the life period between 40 and 50. Thereafter it appears to decline at about the same rate as it rose. Actually, as I have already stated, I believe that it is not the prevalence of the condition which declines, but rather the inclination to seek relief. It should be mentioned that the two women who first had arthritis at the age of seven had suffered for 40 and 45 years respectively before they came under my care.

Table 5

Age at onset	Female	Male	Total		Total
			F	M	
7	2	0	2	0	2
13	0	1			
14	1	0			
15	1	0			
17	0	1			
18	2	0			
20	2	0	6	2	8
21	0	1			
22	2	0			
23	1	0			
24	0	1			
25	1	0			
26	2	0			
27	1	0			
28	2	3			
29	1	0			
30	4	1	14	6	20
32	6	0			
33	1	0			
35	2	1			
36	1	0			
37	3	1			
38	4	2			
40	3	0	20	4	24
41	5	0			
42	3	0			
43	1	0			
44	2	0			
45	2	2			
46	4	0			
47	4	1			
48	3	2			
49	3	0			
50	2	0	33	5	38
51	1	1			
52	4	2			
53	4	2			
54	4	0			
55	1	2			
56	1	2			
57	4	0			
58	0	2			
59	1	0	21	11	31
62	1	0			
66	1	0			
67	1	0	3	0	3
71	0	1	0	1	1
Total	93	29	62	27	127

Table 6
Occupations

Female		Male	
Housework unaided	26) 48	Executive	17
Housework with aid	22)	Medical Practice	5
Social Life	35	Legal Practice	1
Teaching	6	Dentistry	1
Nursing	3	Professorial	1
Clerical work	2	Writing	1
Writing	1	Study	2
Medical Practice	2	Electric Wiring	1
Study	1	Salesmanship	1
	98	Carpentry	1
			29

Comment on Table 6: In a previous publication (1) I stated that it is commonly accepted that certain individuals have a predisposition to joint affections, and those who attribute the occurrence of arthritic lesions to trauma base their opinion on the fact that the joints most exposed to injury are those most likely to be affected by arthritis. That this conception is erroneous, might be surmised when we consider how universally man and all other animals are subjected to trauma, yet how far from being universal is arthritis, distressingly common as this affection is. A study of the foregoing table brings further evidence that trauma plays no important part in the production of arthritis. Not only do women outnumber men, who generally speaking, pursue occupations where trauma is a much more constant hazard, but with the possible exception of the electrician and the carpenter, even the men were not engaged in occupations where trauma would play any conspicuous part.

Considering females alone, the houseworkers—48 all told—were by far the largest subdivision; next to this comes the group of women who are freed from all traditional "woman's work," but in the more or less hectic "social life," with its late and irregular hours, indiscretions in diet and nervous strain, actually undergo more physical exhaustion than those who are called upon to do the manual labor involved in housework. Thirty-five cases are included in this group. The third group, numerically considered, is that of teachers, which includes 6 cases. Houseworkers thus make up almost 50 per cent of all female cases; those engaged in social activities 36 per cent; and teachers something less than 6 per cent. This is probably of no especial significance except to show that my group of women afflicted with arthritis is very representative of the occupational status of women generally, as despite much literary outcry to the contrary, far more than half our women are still "in the home," and those who are engaged in gainful occupations are still to be found more often in the traditional female employments of teaching and nursing.

More than 60 per cent of my male patients were in executive positions, making the largest single group of male patients, and exceeding by 10 per cent the relative size of my largest female occupational group. Contrasting these two largest groups, we may note that the houseworker is required to expend both physical and mental energy, whereas the executive employs his brain largely to the exclusion of his muscles in the pursuit of his means of livelihood.

SUMMARY OF PERSONAL STATISTICS

1. Arthritis may appear at any age, but there is a progressive increase in the number of cases appearing as age advances, reaching a maximum in the sixth decade, with a marked decrease in the seventh and eighth decades.

2. In this series, 92 per cent of the cases originated in the age period included between 31 and 69 years.

3. The duration of the condition before the patient came under my observation ranged from six months to 45 years; 27 patients had had arthritis for 10 years which was the largest number for any single duration period. In the two- and three-year periods there were 12 patients each.

4. The proportion of females to males was 3.4 to 1.

5. Housework and social life occupied the largest group of female patients, this being the largest occupational group of the entire series.

6. Executives made up the largest male occupational group, this corresponding relatively closely to the position of houseworkers and socially engaged among the female patients.

ANATOMICAL DISTRIBUTION OF THE AFFECTION

One of the strongest arguments in favor of the traumatic theory of the etiology of arthritis has always been its prevalence in the joints of the hand. My series followed precedent in this respect, for of the 127 cases, the fingers were affected in 92 patients. But, as already pointed out, few of my patients were in occupations which especially subjected them to trauma, and moreover but few of the histories obtained made trauma of any variety a likely etiological factor. The location of the joint affection in its order of incidence is given in Table 7. It will be seen, of course, that many patients fall into several of these classifications, and that 37 were affected in all the joints of the body.

Table 7
Joints Affected with Arthritis

Fingers	92 cases	Ankles	54 cases
Knees	87 "	Wrists	51 "
Shoulders	70 "	Cervical Vertebrae	44 "
Feet	62 "	Sacroiliac	39 "
Elbows	60 "	Lumbar Vertebrae	39 "
Hips	56 "	Dorsal Vertebrae	17 "
Having all joints affected		37 cases	

In addition to trauma a good deal of stress has always been laid on the protection from the effects of moisture and changes of temperature afforded to those joints generally covered by clothing. A glance at the preceding table indicates that, in my series at least, unprotected joints—excepting those of the hand—seem to suffer equally with those which enjoy more or less protection. The knee joint which was—after the fingers—that most frequently affected, offers a considerable flat area which is readily traumatized, and also because of its position and function is frequently subjected to sudden jars and twists. I believe that these factors might favor affection of this particular joint in one otherwise predisposed to arthritis. As regards protection by clothing, while I do not consider exposure as a primary etiologic factor in the production of arthritis, it too, may be a contributing cause where predisposition already exists.

It is of interest to notice that the ankles and wrists were about equally affected. Neither of these joints enjoy much protection from the clothing. The ankle receives more strain while the wrist has a wider range of movement. Lumbar and sacroiliac joints were affected in exactly the same number of cases, while the cervical was a somewhat more common site of arthritis, and the number of dorsal cases was distinctly lower, being less than two-fifths of the number of cervical cases.

The type of joint does not seem to have any great bearing upon the incidence of arthritis. While the wide range of movement of a semi-ball and socket joint, such as the shoulder, may account for that joint being third on the list, the similar joint at the hip ranks sixth, although in this joint there is probably more chance of strains, twists and injuries, though a less wide range of movement. Again, the elbow joint anatomically bears a close resemblance to the knee and is capable of greater flexibility, but in this series shows a decidedly smaller incidence of affection.

In Table 8 will be found detailed the joints first affected in the different cases. In general affection was bilateral, but there were a number of rather noticeable exceptions. On one of the 92 finger cases one thumb alone was involved; there was one case of affection of a single wrist; three elbow cases involved the right side only, and one the left side only; there were six patients affected in the right shoulder only, and one in the left

Table 8
Joints first affected.

Fingers	Wrists	Elbows	Shoulders	Feet	Ankles	Knees	Hips	Cervical	Dorsal	Lumbar	Lumbar-Sacral	Sacroiliac
46	4	4	10	16	4	20	10	6	2	6	2	4
Rt. Middle 1	Rt. 3	Rt. 2	Rt. 3	Rt. big toe 2		Rt. 3	Rt. 1					Rt. 1
Rt. Index 3												
Lt. Index 1	Lt. 1	Lt. 2	Lt. 1	Lt. big toe 2	Lt. 1	Lt. 2	Lt. 3					Lt. 2
Lt. Thumb 1												
Fingers and Toes	1		Rt. Wrist and Rt. Shoulder 1			Feet and Rt. Knee	1			Cervical-Dorsal		1
Fingers and Feet	2		Lt. Elbow and Lt. Wrist 1			Ankles and Knee	1			Cervical-Dorsal-Lumbar		2
Fingers and Knees	1		Lt. Elbow and Lt. Knee 1			Knee and Hip	1			General Onset		2
Fingers and Wrists	1					Lt. Knee and Rt. Shoulder 1						
Fingers and Elbows	1					Rt. Knee and Rt. Toe	1					

only. As there were no left-handed persons in this series one would look for a greater incidence of right-sided affection if trauma and strain were important etiological factors in the production of arthritis.

Most of the patients had a number of joints affected before they came under observation. However two patients had only a single shoulder involved, and there were one each who complained only of cervical, sacroiliac and ankle joint respectively. In a few cases of multiple joint affection there had been previous trauma to one or more joints and in one case of fracture of the left hip this joint was throughout the most painful and troublesome. Other cases where injury preceded arthritis were: Of the right knee, one case; of both knees, two cases; of injury to the ankle, two cases, one to the right side and one to the left. Of the 92 cases showing involvement of the finger joints it will be noted that 46 or exactly 50 per cent. were first manifested in these joints.

SUMMARY OF DISTRIBUTION AMONG DIFFERENT JOINTS

In general, there is no predilection for any one joint in the incidence of arthritis, but it is noticeable that certain joints are undoubtedly more frequently affected than others.

1. More patients suffered from arthritis of the finger joints than any other anatomical location, and these joints also were the first implicated in the greatest number of cases.

2. The knee joint is second both in frequency of involvement and presentation of the initial lesion of arthritis; the shoulder joint is third in the list of joints most frequently affected.

3. In more than one third of the cases the cervical vertebrae were affected.

4. General arthritis, that is, affecting all the joints, prevailed among nearly one third of these patients.

5. When a joint has been traumatized previous to the onset of arthritis, the joint will be affected, and cause more distress than other not traumatized joints.

6. The protection offered by clothing appears to have no influence in determining the location of arthritis, the knee and shoulder being almost equally affected with such unprotected joints as those of the fingers and neck.

FAMILIAL OCCURRENCE

Of the entire series of cases, 37 patients or 29.1 per cent, gave a family history of arthritis. Some of these findings are set forth in Table 9.

Table 9

Familial Occurrence of Arthritis

Females	29	Mother	Father	Mother and Father	Mother and Grandmother	Mother, Father & Grandmother
Males	8	20	11	3	2	1
	37					

In the entire series the ratio of patients giving a family history to those whose family history was negative for arthritis is about 1 : 3. It will be noted that the mother is the relative most frequently affected; the maternal factor being present in 26 of the entire 37 cases.

Table 10
Familial Occurrence of Associated Conditions

	Asthma	Hay Fever	Urticaria	Eczema	Headache
Mother	1		1		
Father	1	1			2
Mother and Father					1
Brother	2	1		1	
Sister	3		1		

Table 10 is of especial significance in regard to an anaphylactic basis for the incidence of arthritis, to which more attention will be given later.

ETIOLOGIC FACTORS SUGGESTED BY THIS STUDY

Survey of the case histories in this series suggests the following etiologic factors as productive of the arthritic condition: (1) Food; (2) Infection—focal or due to systemic disease; (3) Gastro-intestinal disturbances; (4) Constipation; (5) Exposure; (6) Trauma; (7) Nervous shock; (8) Fatigue.

Food Allergy was suggested by the author as an important causal factor in arthritis several years ago. (1) An illustrative case may be cited. (2)

A married woman of 68 presented ankylosis of ankles, knees, left elbow and shoulder with no motion whatever, the elbow being fixed at a 75-degree angle. There was slight rotary motion of hips; limited motion of right shoulder and elbow. The patient was unable to feed herself or touch any part of face or head. Cutaneous tests gave reactions to wheat, lamb, peas and chocolate. Two months after elimination of these foods from the dietary the patient was able to feed herself, dress her own hair and hold the arm straight above her head for five minutes. In four months she was able to raise her feet from the floor ten inches.

Infections, focal and otherwise, have been cited by many investigators as factors in the production of arthritis. Umber (3) found that it followed bacterial infections in tonsils, accessory sinuses, middle ear and upper respiratory tract, as well as the urogenital and intestinal tracts; and might also accompany general infections in acute disease—scarlet fever, influenza, etc.—or systemic infections of a chronic type, such as tuberculosis and syphilis. Nakamura (4) inoculated animals with hemolytic streptococci from the tonsils of patients suffering with gastric ulcer and arthritis, and found that the organisms tended to localize in the gastric mucous membrane and the joints. Organisms from the tonsils of normal persons showed no such localization, which led him to believe that such streptococci are important agents in the production and persistence of gastric ulcer and arthritis. Billington (5) thinks that for practical purposes, a very high percentage of rheumatic manifestations may be regarded as metastatic phenomena due to focal bacterial absorption. In this series the removal of supposed foci of infection many times had no effect whatever upon the arthritic condition, and it seems likely that such removal may at times serve rather to "light up" a hitherto more or less quiescent infection.

Infected Tonsils as a Causative Factor: In this series 37 patients had already undergone tonsillectomy when they came under my care. Of the 90 patients still in possession of their tonsils, 38 or 42.2 per cent had some caseous exudate; in 15 it was abundant, in 13 moderate

and in 10 very small in amount. None of the patients previously tonsillectomized had experienced any amelioration of their arthritis. In 17 cases the tonsils had been removed without their presenting any pathologic symptoms, merely on suspicion that the arthritis might be due to some hidden infection which they were harboring. In 20 cases there was a definite history of tonsillar disease. Of the patients who still had their tonsils, an investigation of the throat showed no caseous exudate, a number showed distinct tonsillar pathology, such as hypertrophy, submersion, or overlapping of the pillars. It seems reasonable to suppose that in the 17 cases where no tonsillar pathology was in evidence, the unnecessary shock, general systemic disturbance and lowering of resisting powers, may very well have had the effect of increasing the arthritic manifestations. These 37 failures may be taken as evidence that although the source of tonsillar infection may have been removed, even if the joints were originally infected from this source, other factors were active to continue and intensify the arthritic process.

Dental Infection as a Causative Factor in Arthritis: Fifty-five, or 40.1 per cent of all the patients in this series had had all or a portion of their teeth removed before coming under observation. Some gave a history of definite dental involvement, but others had merely had the teeth removed "on general principles," in the hope that the source of the arthritic infection might thus be eliminated. In but three of those examined were foci of infection found about the teeth; 76 or 55.5 per cent of the entire series of cases showed some evidence of pyorrhea. In the series reported by Stauffer (6) about 10 per cent of the patients showed dental infection. While there is no question about the wisdom of removing teeth definitely demonstrated to be harboring apical abscesses, the wholesale removal of teeth on the mere suspicion that they may be instrumental in the production of arthritis should be most roundly condemned, and in the past has been most grossly overdone. When dental infection is unquestionably present the patient should be informed of the probability of its being a contributing factor in the causation of arthritis, but under no condition should wholesale extraction be practiced unless there is undoubted evidence of infection.

Syphilis as a Predisposing Cause of Arthritis: Chronic deforming polyarthritis of syphilitic origin usually appears in youth, or at the menopause in women. When localized in one joint it may often be mistaken for tuberculosis. Dufour and his co-workers (7) report the case of a woman of 42, whose intense arthritic symptoms and stiffness of most of the joints yielded to bismuth injections, after neo-arsphenamin—suggested by an alternately positive and negative Wassermann reaction—had been abandoned because of severe albuminuria. These authors find the chances of improvement and even permanent cure good, when antiluetic medication is undertaken early enough. The osteitis tends toward atrophy rather than toward hyperostosis. Schlesinger (8) found syphilitic arthritis relatively common, and believes that there is scarcely any form of arthritis which is not stimulated by a coincident luetic infection. In the series here considered

two patients had a syphilitic history, with a strongly positive Wassermann reaction. Both were married women in the fourth decade of life. One came under observation because of a cough and other symptoms thought to be tuberculosis. The diet was modified in accordance with the results obtained from a series of cutaneous tests, and the symptoms all disappeared, the cough, however, returning as soon as the dietary regulations were disregarded. The Wassermann reaction remained positive despite arsphenamin treatment, and three years later the patient returned with arthritis. The diet was again regulated in accordance with a new set of cutaneous tests, and the arthritis was immediately controlled. The other patient's serum gave a consistently positive Wassermann reaction despite treatment with mercury and arsenicals. When first seen she had cutaneous, mucous and tibial periosteal involvement. Four years after the first series of treatments she returned with a history of frequent attacks of severe biliary colic, with periodic gastric hyperacidity and other digestive disturbances. X-ray showed marked thickening of the gall-bladder. Observance of dietary regulations worked out in accordance with the results of cutaneous tests completely relieved the biliary and gastric symptoms at this time. Three years later the patient developed arthritis, but resort to the cutaneous tests and adherence to the foods to which she proved not to be sensitized, quickly abolished the arthritic manifestations. This patient also had congested tonsils, exuding considerable pus. Both women were obese.

The outcome of these two cases, and their prompt relief by dietary measures alone showed that the arthritis was not syphilitic in origin despite the positive Wassermann and the other apparently luetic manifestations. Had the cutaneous tests not been applied it is doubtful if the true nature of the disturbance from which these two women suffered would ever have been satisfactorily cleared up.

DISEASES CO-INCIDENT WITH ARTHRITIS FOUND IN THIS SERIES

Many of the patients in this series were suffering from what I have termed *allied diseases*; that is, affections which are frequently seen in conjunction with arthritis, and many of which have been determined by recent investigations to be allergenic in nature. With them I believe, should be classed certain other affections, the symptoms of which I have repeatedly seen to disappear by elimination of proteins to which the subjects were sensitive. In this class should be placed acne, furunculosis, pruritis and phlebitis.

Table 11
Arthritis and Allied Diseases

Hay Fever	Vasomotor Rhinitis	Cough	Asthma	Total
9	6	2	11	28
Asthma	4 Pruritis 1	Asthma 1	Hay fever	3
Horse asthma	1 Eczema 1	Nasal	Horse asthma	1
Neuritis	1 Syphilis 1	polyps 1	Headache	1

Table 11 shows the allied affections presented by 28 patients of this series. A fair proportion of these patients had more than one allied condition, indicated by name below the larger group of which they form a

part. "Cough" of allergenic origin, I regard as preliminary to asthma, merely depending upon the amount of anaphylactic substances absorbed as time goes on. In Table 12 *headache* as a condition associated with arthritis is separately considered, and the other allied conditions which certain patients presented in addition to arthritis and headache are listed below. Thirty-four patients gave a history of chronic headache, which affected all parts of the head. In some patients the pain began in one area and later involved others, or even the entire head. The character of the pain varied greatly, being reported by some patients as dull and throbbing, by others as sharp, shooting, etc. In some subjects the involved areas were sensitive to palpation.

Table 12

<i>Arthritis Allied with Headache</i>		34 cases
Associated with		
Eczema		3
Urticaria	--	2
Angioneurotic edema	--	1
Hypersensitivity of skin (to sun, wind, etc.)		1
Asthma	...	1
Vertigo	--	1

The type of headache complained of varied widely among the 34 subjects. The duration mentioned ran from a few hours to 24 hours, and in some cases the pain continued for several days consecutively. Again, it occurred at intervals for relatively short periods.

Table 13

Skin Conditions Allied with Arthritis

Urticaria	12	Headache	2
		Eczema	--
		Acne	--
		Vasomotor Rhinitis	1
Acne	4	Headache	1
		Urticaria	--
		Eczema	1
Eczema	18	Headache	4
		Urticaria	--
		Vasomotor Rhinitis	1
		Cough	1
		Asthma	1
		Acne	1
		Syphilis	--
Furunculosis	2	Rhus toxicodendron	1
Psoriasis	--	2 Pruritis	1
Pemphigus	1		

The association of arthritis with various skin conditions has been noted by many authors. Rowe and McCrudden (9) report a case of scleroderma in an arthritic patient, and in three cases of Garrod and Evans (10) psoriasis was associated with arthritis. The case described by Radcliffe (11) began with a painful neuritis, followed by psoriasis, and after the subsidence of the active eruption, arthritic manifestations.

Table 14

Gastro-intestinal Conditions Allied with Arthritis

Indigestion	79	Nausea	2
		Gastroenteroptosis	2
Constipation	37	Diarrhea	1
		Membranous colitis	1
Cholecystitis			3
(One with gall-stones)			

The fact that a patient is suffering from arthritis of allergenic origin does not involve digestive disturbance necessarily. However, 37 of the cases in this series presented constipation, and indigestion is mentioned in 79 histories. Three patients had been subjected to cholecystectomy, gall-stones being present in one case. Gas and abdominal distress were the most constant symptoms; two patients complained of nausea as well. All the constipated patients used laxatives regularly, 17 being so disabled by the arthritis that inactivity aggravated the sluggishness of the bowel. Of the four obese patients, two had become so after the onset of arthritis. It is interesting to compare these findings with those of Carter (12) upon 123 cases of chronic deforming arthritis. He found 81 per cent of gastro-intestinal lesions, and in 15 per cent, some focus of infection in the urogenital tract. In 60 per cent focal infection was demonstrated in teeth, tonsils or nasal accessory sinuses. This author regards the lower alimentary tract as responsible for more infective foci than the more frequently incriminated upper respiratory tract.

Trauma, Nervous Shock, Fatigue and Exposure. As has already been noted, trauma may be a contributing cause in arthritis, but in my opinion can only be effective when an arthritic predisposition already exists. A previously injured joint will be the first affected in most instances, and is likely to be the last one to clear up, always remaining the most easily affected by indiscretions of diet or other arthritis-producing factors.

Shock or other emotional disturbance is undoubtedly of consequence in the production of arthritis. Two of my cases illustrate this: A woman of 65 suffered severe nervous shock from the sudden death of her husband. She remained unconscious for forty-eight hours, her hair becoming gray in a single night. Arthritis supervened shortly, confining her to bed for three months, and preventing her from walking for a year. Another patient, a machine gunner in the World War, was struck by a shell, lay unconscious and wounded in a pool of mud and water for many hours, was captured by the enemy and left lying upon wet straw for some time longer, and finally remained for three months in an enemy hospital where he was treated for wounds and "pain in the back" upon which arthritis promptly intervened.

The connection between arthritis and exposure to inclement weather, remaining in wet clothing or damp houses, or residence in marshy and poorly-drained districts has long been emphasized by laymen and physicians alike. The complaint that stiffness and pain in the joints increases before a storm is very often heard. It appears reasonably well established that rising temperature, increasing humidity and marked lowering of barometric pressure have a certain influence upon the course of arthritis. A warm temperate climate with reasonable altitude is popularly supposed to provide the best conditions for the arthritic, but it is noticeable that even in such "ideal" climates the inhabitants are not entirely free from arthritis, which appears to be found literally from pole to pole. Seeking an explanation of climatic and temperature effects upon joint conditions

it is well to consider a possible dependence upon circulatory disturbance. Four cases in this series presented evidences of circulatory disturbance as shown by Table 15.

Table 15

Circulatory Disturbances Associated with Arthritis

Angioneurotic edema	1 case
Loss of finger and toe nails	1 case
Phlebitis	1 case
Purpura hemorrhagica	1 case

The experiments of Mauwaring and Boyd (13) showed that certain bacterial toxins so affect the capillary endothelium of the perfused heart as to produce marked edema and hemorrhage of the myocardium, dilatation of the tissue spaces and extravasation of numerous red blood cells. Disturbances of the circulation undoubtedly constitute a certain proportion of the underlying pathological change evidenced in rheumatic and arthritic conditions. One patient in this series had suffered from arthritis for twenty years when first brought under observation. The toe joints were the first affected, and coincidentally the nails turned black as if bruised and eventually fell off. Later the joints and nails of the fingers were similarly affected. This was probably the result of interference with the circulation to the matrix of the nail by the joint condition, or may possibly have been a direct effect of the causative proteins upon the walls of the blood vessels through which they were circulated.

FOOD ALLERGY AS A BASIC CAUSE OF
ARTHRITIS

The idea that diet has some definite influence on the course of "rheumatic affections" is by no means new. Although I have not studied Hippocrates in the original sufficiently to discover his opinions upon this subject, it is not unreasonable to suppose that he had them. The difficulty has always been to find out just what foods failed to "agree" with the patient suffering from arthritis. Not until the comparatively recent introduction of the cutaneous tests for protein sensitization were we provided with a procedure by which this knowledge could be regularly acquired.

That inflammation of the joints might regularly be traced to protein sensitization is a logical following out of the path opened by those who applied the cutaneous sensitization tests to affections of the upper respiratory tract such as asthma and hay fever, or of the cutaneous surface, as urticaria and eczema. It appears to be sound reasoning that those disturbances of the joints which we group under the common designation *arthritis* may depend upon the continued action of bacterial or other proteins, either with or without the additional factors of which mention has been made in preceding paragraphs. The combination of such continual protein intoxication with the injurious factors of trauma or movement of inflamed joints may well eventuate in extensive injury to cartilaginous and bony structures.

That food proteins are more important in such causation than bacterial toxins has been amply illustrated by the 127 cases here considered. It has already been stated that 37 patients had undergone tonsillectomy before coming under observation, and that of the re-

maining 90 who still had their tonsils, 38 showed tonsillar pathology of greater or less degree. The tonsils are generally recognized as being the most likely focus of infection in the body, and are therefore, frequently incriminated in arthritis. Yet 26 per cent of my series still sought relief from their arthritic symptoms after the tonsils had been removed. Twenty of these patients experienced relief from pain and other symptoms by restricting themselves to the diet indicated by the results of cutaneous sensitization tests. The results obtained from dietetic treatment of those patients who presented tonsillar pathology both past and present are presented below in tabular form:

Table 16

Dietetic Results in Arthritis in Tonsillectomized Patients

Dietetic Result	Number of patients	Percentage
Relieved of symptoms	20	54.05
Considerable improvement	3	8.11
No change	10	27.03
Unable to trace	4	10.81
	37	100.00

Table 17

Results of Dietetic Treatment of Patients with Tonsils

Result of Diet	Number of patients	Percentage
Relieved of symptoms	55	61.1
Considerably improved	12	13.3
No change . . .	16	17.8
Unable to trace	7	7.8
	90	100.00

Of the entire 58 patients who had, or had had some tonsillar involvement, 33 or 56.9 per cent were completely relieved of symptoms, and 10 or 17.2 per cent, showed decided improvement, making 74.1 per cent who were benefited by dietetic treatment when therapy directed toward the tonsils had failed. This certainly seems to indicate that diseased tonsils are by no means the chief causative factors in arthritis. It would be possible to extend this tabulation to various other supposed causative factors in the production of arthritis, or to elaborate the figures indicating that undue emphasis has been laid upon tonsillar infection as the chief etiologic agent in joint affections. I do not, however, wish to indicate that tonsillar involvement plays no part in the etiology of arthritis. It is of great importance as a contributing factor in every case where it exists and it is, of course, evident that patients suffering from arthritis who had undergone tonsillectomy and been thereby relieved of their joint complaints, would not be included in such a series as this. There remain a certain number of patients who are aware of the possibility of tonsillar infection but through fear of operation or other reason, are anxious to try every means possible to avoid tonsillectomy. Many of these subjects were perfectly relieved after following the diet indicated by the results of cutaneous sensitization tests. It therefore seems reasonable to apply these tests as a routine before resorting to excision of the tonsils, or any other of the drastic measures which are advocated for the relief of arthritis.

SUMMARY

A series of 127 patients is considered as to personal history, length of time they had suffered from arthritis, age at which arthritis was first manifested, and occupation in its possible relation to the etiology of arthritis.

A discussion of the joints most frequently affected shows that arthritis attacks the finger joints most often; the vertebral joints are least often affected; 37 patients were attacked in all joints. Joints protected by clothing do not appear to enjoy any special immunity. A joint previously traumatized will be more severely involved in a general arthritis.

A family history of arthritis was obtained in 29.1 per cent of the cases. The mother was the relative most frequently affected: in 26 of 37 cases. In 15 instances relatives had suffered from allied conditions of anaphy-

lactic origin.

Etiologic factors of arthritis suggested by this study and commonly accepted as of importance are discussed. These are food allergy, focal and systemic infection, constipation, gastro-intestinal disturbances, trauma, nervous shock, fatigue and exposure. Allied diseases, known to be due to protein anaphylaxis, are considered in their relation to the occurrence of arthritis. The popular connection between wet weather and arthritis is possibly due to observation of the effects of circulatory disturbances.

The cutaneous tests for protein sensitization permit the selection of a diet which in most cases will relieve an arthritic patient of all or the greater part of his symptoms. This therapy is so simple and so readily carried out, requiring nothing more than a little self-denial on the patient's part that it deserves a trial in every case presenting arthritic symptoms.

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Notes on Nutrition

The future of nutrition. This war may prove valuable if it hastens the day when, through adequate knowledge and practice of nutrition, there will be freedom from want for all. The earth can produce enough food for all men to eat, but national or international nutritional progress must be directed by men of integrity not by pressure groups. People are becoming food conscious through the work of the Nutrition Board of the National Research Council and even through the system of rationing. We should look to physicians for leadership but unfortunately "the average doctor knows too little about the fundamentals of nutrition, not to mention their application. Often he is only too happy to refer nutritional matters to the dietitian, sometimes with a superior air." The challenging fact today is that we have a starving world. At the present time the prospect of a proper solution of our socio-economic problems seems utopian, but the continuance of enlightening progress in nutrition was never more assured. (Henry A. Mattill, Prof. of Biochemistry, State Univ. of Iowa, Iowa City. Original communication).

Diet, retarded growth and longevity. Restriction of caloric intake increases the life span of rats (*Arch. Biochem.* 2, 469, 481, 1943). Under-nutrition early in

life leads to permanent changes in body tissues which will not permit maximal physical development. (*Anat. Record*, 68, 371, 1937). The incidence of tumors and lung infections is higher in normal than in retarded animals. The lowered incidence of lung infections is the immediate factor responsible for the increase in longevity. The establishment of the exact cause of limitation of growth appears to be an important step in determining the reason for the increased longevity in retarded rats. That life can be lengthened by diet is in itself an important contribution to the study of the physiology of aging.

Nutritional background of patients with rheumatoid arthritis. Red smooth tongue and skin changes similar to those in vitamin B-complex deficiency are often seen in patients with rheumatoid arthritis. Careful dietary studies of 31 patients with the disease (*New Eng. J. Med.*, 229, 319, 1943) showed that in most respects their pre-disease diets were about average for the section of the country in which they lived. Over two-thirds of them fell short of the National Research Council's recommendation for calcium, thiamin and riboflavin and about one-half had an inadequate intake of vitamin C. Most of the individuals had unusual

expenditures of nervous or physical energy prior to the onset of the disease. This produced an increased food requirement, which may or may not be etiologically significant.

Vitamin in meat. It was found that fresh and freshly stored hams were similar in their content of thiamin, nicotinic acid and riboflavine. Average retention during storage is 92 per cent for thiamin and nicotinic acid 85 percent for riboflavine (J. Nutrition, 26, 73, 1943). In the curing process, 73 percent of the thiamin, 84 percent of the nicotinic acid and 92 percent of the riboflavine were retained. After roasting, the average total retention in the meat, plus drippings, was 70 percent for the thiamin, 96 percent for the nicotinic acid, and 84 percent for the riboflavine. After frying, the average total retention in the meat, plus drippings, was 92 percent for the thiamin, 96 percent for the nicotinic acid, and 86 percent for the riboflavine. The relatively high retention during frying agrees well with previous work. An investigation of the biotin content of meat (J. Nutrition, 26, 65, 1943) showed that pork loins and hams contained 50 millimicrograms of biotin per gram of fresh tissue. An average of 80 percent of the biotin was retained in the meat, plus drippings, after cooking. Kidney and liver were found to be the richest sources of biotin.

Microbiological determination of nicotinic acid. For modifications in the Snell-Wright microbiological method for the estimation of nicotinic acid, the work of Krehl, Strong and Elvehjem (Ind. Eng. Chem. (Anal. Ed.) 15, 471, 1943) should be consulted.

Effect of preparation and cooking on the vitamin content of dehydrated foods. It has been known for some time that considerable loss of vitamins, especially thiamin and ascorbic acid, occurs when improper methods of cooking are employed. (Nutrition Reviews 1, 56, 320, 1943). Potatoes may lose as much as 90 percent of their ascorbic acid if allowed to stand for 30 minutes after mashing. Dehydrated foods present new problems as to the best ways of preparing them. Recent work (Am. J. Pub. Health, 33, 799, 1943) shows the losses during cooking of the dehydrated vegetables,—beets, cabbage, potatoes and rutabagas. Increasing the amount of cooking water from a minimum for each vegetable resulted in a marked and consistent decrease in the amount of thiamin retained in each vegetable and a corresponding increase of the amounts lost in the cooking water. In cabbage, 71 percent of the ascorbic acid was retained when the initial temperature of the cooking was 98° C, and only 28 percent retained when the initial cooking water temperature was 20° C.

Skin changes and vitamin A deficiency. Follicular hyperkeratosis is now admitted to result from vitamin A deficiency. From recent work it appears that this cutaneous manifestation is increasingly present with advancing years, being rare in infancy, and marked at puberty. (Arch. Dermat. Syph. 48, 1, 1943). The integrity of the pilosebaceous tissues in the presence of vitamin A deficiency is thought to be closely related to sexual development. There is a similarity between the epithelial changes produced by vitamin A deficiency and those produced by the physiological

action of estrogenic substance on the vaginal mucosa. Both induce hyperplasia and keratinization of epithelium. This suggests that the disturbed cellular metabolism may depend on the same, or closely related, biochemical faults. The increasing function of the sexual glands may play a part in conditioning the pilosebaceous structures to respond more readily with a keratinizing metaplasia or hyperplasia of epithelium.

Recent work which attempts to find the cause of Darier's disease (keratosis follicularis) in a deficiency of vitamin A, is not perfectly convincing in spite of some good therapeutic results, using vitamin A. Chiefly lacking is proof of vitamin A deficiency prior to treatment (Arch. Dermat. Syph. 48, 17, 1943).

Carotene and ascorbic acid in peppers. (Lantz Bull., No. 306, 1943, New Mexico Agricultural Experiment Station at State College, New Mexico). The epitome of this recent work on chili peppers is to the effect that they are good sources of vitamin C and carotene, and usually contain largest amounts of both when ripe or nearly ripe.

Gastric lesions caused by calcium deficiency. Hemorrhagic erosions in the fundus, and epithelial hyperplasia with central areas of necrosis in the antrum and rumen of the stomachs of rats were produced by diets deficient in calcium (Proc. Soc. Exp. Biol. Med. 53, 34, 1943). This nutritional gastritis in rats shows that calcium intake must be investigated in all cases in which such gastritis is encountered.

Niacin and necrotic enteritis in swine. Necrotic enteritis, characterized chiefly by diarrhea and emaciation, and, in the final stages, by inflammatory lesions of the colon, accounts for much of the high mortality in young pigs. By some this disease is regarded as the "pellagra of swine", and is due to niacin deficiency, while many veterinary pathologists regard the disease as due to infection with *Salmonella cholerae suis*. (J. Animal Sci. 2, 138, 1943). At all events, sulfaguanidine and niacin offer the best form of therapy in the necrotic stage.

Vitamin A requirements of infants. An infant may have good dark adaptation, signifying a good retinal quota of vitamin A, yet show a deficiency as judged by the plasma level of the vitamin. Probably infants require a daily intake of 100 to 200 international units per kilogram to maintain normal plasma levels. (Proc. Soc. Exp. Biol. Med. 52, 265, 1943). Plasma levels constitute a better guide than the amount needed to maintain dark adaptation, for the retina stores vitamin A and suffers deprivation relatively late in states of deficiency. In rats, maximal retinal concentrations could be maintained on only 2 units per day, whereas normal growth required 25 units per day, and the maintenance of normal plasma levels required 50 units per day (Proc. Soc. Exp. Biol. Med., 46, 248, 1941; J. Nutrition 23, 351, 1942). Similar findings have been obtained for infants (Am. J. Dis. Child. 62, 1129, 1941). The optimal daily dose for infants to maintain normal plasma levels lies between 600 and 1200 units. Febrile conditions, however, may necessitate temporarily raising the intake.

Raucidity in experimental diets. Where experimental diets are prepared and kept at room temper-

ature for several weeks, fats may become rancid, a fact which interferes with the preservation of vitamin E. Oxidation is more likely to occur where crystalline B-vitamins are used in place of yeast, the latter protecting against oxidation (J. Nutrition 26, 43, 1943) (Proc. Soc. Exp. Biol. Med. 53, 176, 1943) (J. Biol. Chem. 147, 515, 1943).

Metabolism of radioactive iron, manganese and cobalt. Using radioactive forms of these elements, both orally and by injection, some light has been thrown on the questions of storage and excretion. The amount of iron absorbed by the gut is in some way regulated by the state of the body's iron reserve. (J. Biol. Chem. 147, 749, 1943). Pregnant women usually absorb two to ten times as much iron as non-pregnant women (J. Exp. Med. 76, 15, 1942). Passage of iron through the gut is slower in anemic rats, and this may be referable to the hypotonicity of the G.I. tract in anemic animals (J. Biol. Chem. 134, 27, 1940). There was a 30 percent retention of iron in normal, as compared with 50 percent retention in anemic rats. Greatest retention is in bone-marrow, blood and spleen. The bile is the most important channel for the excretion of body manganese (Proc. Nat. Acad. Sci. 26, 448, 1940). Cobalt is an essential trace element in sheep and cattle, the cow requiring but 1 mg. per day. Cobalt is excreted chiefly by the urine (Proc. Nat. Acad. Sci. 27, 153, 1941).

Bound pantothenic acid. It appears likely that some 80 percent of the pantothenic acid in blood is present in a combined form that is precipitated by protein precipitants (J. Biol. Chem. 147, 261, 1943). The contention that the bound pantothenic acid might be functional in an enzyme system receives probable support in recent experiments, suggesting that pantothenic acid participates not only in glucose utilization but also in the metabolism of pyruvate (J. Biol. Chem. 142, 445, 1942) (J. Biol. Chem. 145, 237, 1942). The role of coenzyme already has been established for thiamin, riboflavin and niacin.

The American breakfast and midmorning hypoglycemia. One of the important practical problems of everyday nutrition is the selection of a diet which will provide the maximum degree of efficiency among workers. Efficiency experts have long recognized the desirability of supplying "between-meal" nourishment to maintain the performance of office and factory personnel throughout working hours, and the appearance of a "lunch wagon" once or twice during each eight hour shift has become a common sight in many of the factories in this country. Under present circumstances, however, it often has not proved possible to provide the facilities or time necessary for these supplementary feedings. Thorn, Quinby, and Clinton (Ann. Int. Med. 18, 913, 1943) point out that the typical American breakfast—relatively high in carbohydrate and low in both protein and fat—predisposes to midmorning hypoglycemic symptoms and potentially, therefore, might interfere with morning work capacity. They recalled the investigations of Conn and Newburgh (J. Clin. Invest. 15, 665, 1936) which demonstrated that blood sugar levels fluctuated rather widely following the ingestion of a high carbohydrate meal but were rela-

tively stable after the ingestion of a meal high in protein. Conn and Newburgh used diets which provided equivalent amounts of theoretically available glucose; the high protein feeding, however, contained approximately twice as many calories. Because of these considerations, Thorn and associates undertook to determine what effect isocaloric breakfasts containing different proportions of carbohydrate, fat, and protein would have on blood sugar levels, the metabolic rate, and caloric distribution.

The study was made on a normal male subject who had been retained for respiratory studies. During the forty-eight hours prior to each experimental period, he was fed a diet composed of carbohydrate 304 g., protein 69 g., and fat 113 g. (2509 calories). After a fourteen hour fast, determinations of the blood sugar, standard metabolic rate, respiratory quotient, and urinary nitrogen excretion were made. The subject then ate one of the three test breakfasts. At hourly intervals for six hours thereafter, samples of blood, urine, and expired air were obtained for analysis. Each of the three test breakfasts used provided 400 calories and were constructed so that one was high in carbohydrate (82 g.), one high in protein (55 g.), and the third high in fat (32 g.). The actual foods used in the high carbohydrate meal were orange juice, cornflakes, sugar, bread, butter, jelly, and milk. The subject remained in bed throughout the six hour experimental period.

The most interesting changes noted were in the blood sugar curves. A definite increase in blood sugar occurred in one hour after the ingestion of the high carbohydrate breakfast, but the level fell to 69 mg. per 100 ml. at the end of two hours. Only a slight increase was obtained at the end of three hours and the return to normal values was slow. Hunger and weakness developed between the second and third hours. In contrast to this result, a normal blood sugar level was maintained throughout the six hours when the high protein meal was administered, and the subject had a definite sense of well-being during the whole of that period. Following the high fat breakfast, the blood sugar level fell slowly to a level of 71 mg. per cent in five hours; the sensation of hunger was experienced at this time but hypoglycemic symptoms were definitely less than they had been following the high carbohydrate meal. The metabolic rate increased sharply one hour after the high carbohydrate breakfast but returned to the basal level within two hours. After the ingestion of the high protein meal, the metabolic rate remained elevated for the whole experimental period. The high fat feeding had little influence on the metabolic rate.

Furthermore, when analysis was made of the differential derivation of calories after each of the three breakfasts, it was discovered that one hour after the high carbohydrate feeding there was a decided increase in the percentage of calories derived from carbohydrate but this changed rapidly so that most of the calories came from fat metabolism during the last half of the experimental period. The authors point out that many individuals probably do not have the ability to effect a rapid and smooth transition from a metabolic rate in-

volving the utilization of carbohydrate to one utilizing fat as the major source of energy, and hypoglycemic symptoms may occur during the transition. After the high protein breakfast, there was a sustained increase in the percentage of calories derived from protein; a corresponding decrease was noted in the calories derived from carbohydrate whereas those from fat changed but little. Following the high fat meal, more calories were derived from fat and fewer from carbohydrate; no significant change occurred in those coming from protein.

Thorn, Quinby, and Clinton, therefore, have demonstrated rather clearly that the ordinary American breakfast which is predominantly high in carbohydrate may lead to hypoglycemic symptoms during the mid-morning. They have also indicated that an isocaloric meal high in protein would maintain normal blood sugar values and provide a sustained increase in metabolic rate. The implication is obvious, but high protein foods at present are at a premium. The authors make the practical suggestion that increased protein, however, may still be provided by increasing the consumption of foods like milk, cottage cheese, nuts, and soybean products. Attention should be directed to the fact that the observations reviewed here were made on

only one subject, and wide individual variations in response must certainly exist. The value of the study would have been augmented greatly if similar data had been obtained on a subject who performed a standard work test during the experimental period. It is obviously important to learn whether normal activity would accentuate the hypoglycemic response.

Fetal-maternal relationship of vitamin A and carotene. Vitamin K, but not prothrombin, passes readily from mother to fetus, across the placenta. Iron diffuses into the fetal circulation, so that treatment of an iron deficient mother not only cures her anemia but prevents her from giving birth to an infant with inadequate iron stores. In the case of vitamin A, such is not the case, for the fetal concentrations of blood vitamin A appear to be quite independent of, and uninfluenced by, those of the mother. (Am. J. Obstet. Gyn., 46, 207, 1943) (Bull. Johns Hopkins Hosp. 73, 132, 1943).

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Book Reviews

Tratamiento Dietetico De Los Gastrectomizados. By Norberto M. Stapler. M. D. pp. 107. "El Ateneo". Buenos Aires, 1943.

This book, "The Dietetic Care of the Gastrectomized Patient", was written not as a study of "the diseases which appear as sequels to gastrectomy but to disclose the benefits already derived from gastric surgery and to enhance them by analyses of the dietetic requirements." In this attempt the author succeeds rather well. In this slender volume Dr. Stapler has turned out a well-rounded and logical exposition of the subject. A review of the normal physiology of the stomach and intestine precedes an account of the alterations in their functions which are brought about by gastrectomy. Attention is next directed to a study of the common foods and their influence on gastrointestinal activities. Finally the dietary regimen is considered. Sample menus are offered with due attention being paid to necessary modifications to suit individual cases. The main aim in the preparation of the various diets is to make them "sufficient and harmonious" for the organism. A bibliography of 44 items is appended; some of the authors' names are misspelled.

Allergy. By Erich Urbach, with the collaboration of Philip M. Gottlieb. (\$12.) pp. 1,073, with 396 illustrations. New York: Grune and Stratton, 1943.

This book on allergy has its subject matter arranged as follows: part I deals with the fundamentals of allergy and principles of diagnosis and treatment, part II discusses the entire range of etiologic agents, and part III is devoted to symptomology, diagnosis, and therapy of all known allergic diseases. Each section is

complete and thorough and exceptionally well illustrated. It is a book on allergy which at present is without an equal. Anyone especially interested in allergic conditions should read it, and those physicians who do not specialize in the field but occasionally attempt to handle these cases should find it a very helpful and reassuring book. The readers of this particular Journal may find that the author's faith in desensitization through the gastrointestinal tract has a special appeal to them. It is our understanding, however, that the majority of the specialists in allergy do not share the authors' faith in hyposenitization by the oral route, especially as it concerns "propetan" therapy. It certainly appears to be based on uncertain physiological principles.

The fact that the author does not hesitate to express his own opinions is announced in the preface. It seems to us that he projected his own ideas into some subjects he could have better left alone or else dealt with lightly, while in other instances he missed excellent opportunities to give play to his intellectual capacity. We have in mind for a missed opportunity his classification of hypersensitiveness. Here were included among others the terms pathergy coined by Roessle, the parallergergy of Moro and Keller, the metantigen of Centanni, and the heteroallergy of Dujardin and Decamps. The term pathergy, by its very derivation, is too general to come into widespread use. While the author is to be congratulated on the self-restraint shown in not coining new words, we credit him with being capable of devising better terms had he taken this liberty.

It would be possible to list innumerable instances dealing with controversial subjects which the author might have treated less extensively. This is especially true of the very last portion of the book, where the author attempts to include *all* known allergic disease. It must be said, however, that though the reader may not always agree with Dr. Urbach's interpretations (and experiences), he must credit him with presenting both sides of the case. This procedure provides interesting and informative reading.

In some respects the book possibly does not possess characteristics which may be attributed to it at first glance. Over 2,000 references are listed as footnotes and referred to in the index of authors. Bennet, with no initials given, is listed as being quoted on pages 416 and 941. He or she is mentioned on these pages but no journal reference is given. The same applies to Marshall, who is quoted on page 89 and Rich and Follis on page 104. An H. C. Berger is listed in the index as being quoted on page 974 and actually is, but as H. Berger, while on page 414 a reference is given of H. C. Berger but it is not listed in the index of authors.

Aside from such minor errors, which will no doubt be checked in a future edition (and we predict the book will be in demand for future editions), the book is expertly assembled, well illustrated, and will be received with the interest it deserves. In brief, it is heartily recommended.

Allergy, Anaphylaxis and Immunotherapy: Basic Principles and Practice. By Bret Ratner, (\$8.50), pp. 834, with 88 illustrations. Baltimore: Williams and Wilkins Company, 1943.

The author explains in the preface that in undertaking to write a book about allergy in childhood, he discovered that his ideas on serum sickness and its relation to allergy were vague. Apparently, he thereupon assumed many other clinicians were in similar state of ignorance and would probably profit by the reading and investigation he had done for his own enlightenment. It is doubted, however, that many of those who slept through the lectures on this subject during their college days will be willing to make the effort required to read this or any book on the subject of allergy and to understand and comprehend it.

The book is a curious combination of oversimplification of the elements of the subject of allergy and a scholarly presentation of the most recent and advanced studies on the subject. In the first part the author discusses the materials used in diagnosis, prophylaxis and therapy of infectious diseases and immunotherapy. He lists the infectious diseases discussed in alphabetical order, with the result that black-widow spider poisoning and the common cold are in one chapter, syphilis and scarlet fever in another, smallpox and snake bite in still another. Listed separately are anaerobic infections and tetanus; also, Ritter's disease is discussed on equal footing with genito-urinary tract diseases, rickettsial diseases and streptococcal infections. This confused state of affairs is typical of the first part of the book.

The second part of the book considers allergy and

immunotherapeutic agents. It departs from the standard taken by earlier textbooks in not restricting the occurrence of anaphylaxis to animals, and gives case reports of its occurrence in man. A chapter is devoted to drug allergy, but is concerned only with the misuse of the sulfonamides. A number of photographs are found in this section, all of which are blurred and poor.

The third part of the book is on the allergic state, its physiological pathology, blood chemistry, cytology and basic mechanisms. This part is exceptionally good.

The book contains an extensive bibliography. There are numerous charts and passages taken directly from other books and articles. On the whole this adds to the book but it occasionally is disastrous, as in the case of the obsolete classification of streptococci taken from Zinsser and Bayne-Jones. This is especially curious in that the author speaks of the pneumococcus types and yet ignores the Lancefield classification of streptococci.

The book is written in the first person and frequently is conversational in style. This makes for a readable text. With due regard to some errors and misstatements, the book should prove useful to every physician interested in the important subject of allergy.

Biochemistry of the Fatty Acids and their Compounds the Lipids. By W. R. Bloor, pp. 387, (\$6.00). New York: Rienhold Publishing Corporation, 1943.

Professor Bloor is a noted authority on the biochemistry and physiology of fats and their derivatives and much of our present-day knowledge we owe to work by him and his collaborators. This book fulfills a great need. While proteins and carbohydrates received a great deal of attention in the past, the fats were neglected. However, as this book reveals, the gap in our knowledge is rapidly being filled.

The book is divided into six chapters, each of which is a compact section reviewing a definite phase of the subject. The first chapter covers the descriptive and analytical chemistry of the fatty acids and lipids and presents both macro and micro methods for their determination. Chapter 2 will probably be found the most interesting to the gastroenterologist. It deals with the digestion and absorption of fats. Professor Bloor steers clear of becoming involved in the controversies regarding the mechanisms of fat absorption; his account is presented impartially. Some recent work, particularly that by Fitzgerald, has been omitted. The lipids of blood forms the topic of Chapter 3. Actually this is a closely packed section of 85 pages dealing with blood lipids in normal and pathological states. Chapter 4 deals with the lipids of tissues and includes data on various animals, plants and microorganisms. Chapter 5 is of interest to the biochemist, physiologist and internist alike; it covers the important subject of lipid metabolism. The lipids of secretions and excretions forms the context of the final chapter.

It is obvious that a great deal of work went into writing this book. The board of editors of the American Chemical Society are to be complimented on the choice of the subject and the man to write about it, and Professor Bloor is to be congratulated on a job well done. The bibliographical list is fairly extensive and is representative rather than exhaustive. An overall author's index would have been helpful.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

PAUL, L. W.: *Röntgenologic aspects of acute and chronic esophagitis.* (Radiology, 41: 421, Nov. 1943.)

Acute ulcerative esophagitis is common in necropsy specimens but is unusual in clinical practice. While mild forms of esophagitis may be relatively common, they are transient and seldom serious. While the etiology is uncertain, a number of factors enter the picture, such as frequent vomiting, use of stomach tube, trauma and shock associated with abdominal operations, and anatomical changes as esophageal hiatal herniae. The negative suction tube has seldom, if ever, been responsible if the patient survived the disease for which he had been treated. Clinically, it is seen most commonly in association with peptic, particularly duodenal ulcer. The roentgenologic findings in acute ulcerative esophagitis are: (1) lesion largely confined to lower half or third, (2) severe intermittent spasm, (3) fixed deformity within several weeks, probably due to fibrosis, (4) absence of normal mucosal folds with finely irregular margins, (5) progression to complete stenosis. The deformities and stenosis are the common findings in chronic esophagitis.—William D. Beamer.

STOMACH

WOLF, S.: *The relation of gastric function to nausea in man.* (J. Clin. Invest., 22, 877, Nov. 1943.)

Using three normal subjects and one with a gastric fistula, 25 experiments were performed with observations of gastric motility, in 10 of which there was further observation of forehead sweating (measured by skin resistance), pulse and facial color as well as symptoms. The fistula allowed measurement in one subject of gastric blood flow (by color changes), secretion, and salivation in a blind oesophageal pouch. Nausea was induced by various vestibular stimuli as well as by the production of fear and withdrawal reactions in one subject. Discomfort varied with the time and intensity of stimulation.

Cessation of gastric motor function was found to antedate all other bodily changes, and to appear with stimuli insufficient to produce discomfort. Stronger stimuli caused reduction in acid output, increase in output of mucus, and mucosal pallor. More widespread, autonomic effects were associated with abdominal discomfort, nausea and apprehension, but not always with vertigo. Swinging, rhythmic head rotation,

and ingestion of mustard in water produced much the same effects as caloric vestibular stimulation.

Atropine and prostigmine, administered together in sufficient dosage to stimulate and maintain vigorous gastric motor activity, were found to prevent nausea in the presence of vertigo and nystagmus, and to have none of the undesirable side effects of either drug administered singly. The prophylactic possibilities of these drugs in seasickness is suggested.—B. C. Riggs.

BOWEL

SMITH, L.: *Pelvic appendicitis.* (Virginia Med. Monthly, 70, 366/, July 1943.)

Pelvic appendicitis has a tendency to early rupture and to rapid spread of peritonitis. It has the history of an abdominal appendicitis but the physical examination is very unusual. These are a relaxed abdomen and only a generalized lower abdominal soreness, with no localization of pain, or rebound tenderness. There is frequency of urination or in some cases the desire to defecate. Rectal examination is all important and it is here that we find tenderness on pressure over the cul-de-sac and often a definite tender mass. Repeated rectal examinations should be done. Generally, we must exclude rupture of an ovarian follicle and stone of the lower ureter. Correct diagnosis follows careful evaluation of abdominal and rectal examinations with laboratory findings and clinical history.—John J. Cox.

ESTES, W. L.: *Early diagnosis of cancer of the colon.* (Penn. Med. J., 46, 1139/, Aug. 1943.)

As cancer of the colon grows slowly and metastasizes late it is quite favorable for cure by radical surgery. Nevertheless as it frequently is diagnosed too late for resection, the author presents a review of cases to clarify its early diagnosis. In forty cases proven to be carcinoma of the colon, 85 per cent gave as the first complaint constipation associated with abdominal pain. Three hundred cases reported by Swinton and Higginbotham showed, 1) 80 per cent of all cancers of the large bowel show altered bowel function, 2) rectal cancer exhibits altered bowel function with abnormal stools in 86 per cent of the cases, 3) in left and right colon cancer the altered bowel function is associated with abdominal cramps and pain.

Consequently patients giving these complaints were thoroughly examined for cancer of the colon, the examination including: 1) Bimanual rectal and pelvic

examination, 2) Sigmoidoscopic examination, 3) X-ray study—barium and contrast enemas, 4) Tests for occult blood in the stool, 5) Peritoneoscopy if indicated.

As a result of these examinations the resectability rate for cancer of the colon increased from 45 to 85 per cent which is a great increase in those in whom a radical resection could be undertaken with a chance for a cure.—Glenn Clements.

HORTON, H. S.: *Postoperative ileal distension: The problem and its management.* (*Western J. Surg. Obst. Gyn.*, 51, 368, Sept. 1943.)

The report is presented in two parts: first, the problem and second the management. Under the first part, the various etiologic factors which enter into its production are discussed. Surgery of the abdomen, which involves opening the peritoneum, is accompanied by intestinal paresis and inhibition of diaphragmatic movement. This paresis may extend for several days passing into paralysis. Other pathogenic factors of paralytic ileus are peritonitis, renal attacks and gallbladder colic, ovarian cyst torsion, trauma to the abdomen, embolism and thrombosis of the mesenteric vessels, injury to the central nervous system. Vomiting following ileus is a serious complication, since the loss of the various gastro-intestinal fluids may lead to changes in the body chemistry with results which are incompatible with life. The means of distinguishing between high and low intestinal obstruction are pointed out. Under management, the prophylaxis and early recognition of the condition is emphasized. Continuous gastroduodenal aspiration is the most valuable single means of treatment. It is extremely important to differentiate between the presence of actual obstruction and strangulating obstruction, since in the latter there may be extensive necrosis of the bowel wall with toxemia and death. The use of suction alone in such cases can be dangerous, as is also the use of drugs which increase intestinal motility.—H. N. Metzger.

KAJDI, L. AND DAVISON, W. C.: *Chemical and enzymatic studies of the duodenal contents of infants.* (*J. Pediat.*, 23, 204, Aug. 1943.)

Determinations on duodenal contents shown to be free of gastric juice, in 11 cases including diarrhoea, sprue and convalescents from various diseases but with normal digestions, were: specific gravity (by simple weighing or pycnometer); surface tension relative to water (by stalagmometer because the authors felt this more representative of the dynamic state of affairs found naturally than static force gotten by the ring method); bile acids by Raue's method; pH colorimetrically; trypsin and amylase viscosimetrically. Complete tables are given of numerous determinations at various times relative to feeding, symptoms, etc. Diarrhoea was found to be associated with reduction of trypsin and amylase. However, surface tension was found to be quite constant in all cases, in spite of variations in bile acids, rate of flow, etc.—B. C. Riggs.

GLOVER, D. M. AND GARVIN J. B.: *Multiple congenital anomalies with intestinal obstruction.* (*Ohio State Med. J.*, 39, 734/, Aug. 1943.)

Intestinal obstruction due to congenital anomalies is not common. The early recognition of such condition is important because some of them are amenable to surgical care. A case of intestinal obstruction in a week-old infant due to constricting bands of adhesions is reported, with correction of the obstruction and recovery and progress of the patient. An interesting feature was the presence of a loop of jejunum through a hole in the mesentery and partial volvulus of the unrotated cecum.—H. N. Metzger.

SPRAGUE, P. H.: *Functional disorders of the intestine and their management.* (*Can. Med. Assoc. J.*, 49, 105/, Aug. 1943.)

It is now generally considered that the various types of functional bowel disorders such as mucous colitis, spastic colitis, unstable colon, cathartic colitis, irritable colon are all synonymous, and that the basic disturbance is an underlying nervous instability. Experimentally, the local application or the parenteral administration of cholinergic drugs is capable of producing the sigmoidoscopic picture seen in "mucous colitis." Large doses of acetyl-B-methylcholine chloride would cause diarrhea and symptoms not unlike those seen in the so-called irritable colon. This is also true of prostigmine. Apparently, overstimulation of the parasympathetic system is responsible for the production of these symptoms. An emotional tension is present in the large majority of these patients, and in addition, certain personality characteristics are found. As a group they are overconscientious, and any threat to their ego may produce a conflict in the emotional pattern with translation of the nervous stimuli into somatic changes. The management of these cases consists, first of all, in ruling out the presence of any organic condition. With the reassurance of the patient from this standpoint, the physician is then in a position to treat the patient from a psychotherapeutic and symptomatic angle.—H. N. Metzger.

PANCREAS

MADDOCK, C. L., FARBER, S. AND SHWACHMAN, H.: *Pancreatic function and disease in early life: II Effect of secretin on pancreatic function of infants and children.* (*Am. J. Dis. Child.*, 66, 370, October 1943.)

Twenty-six analyses of duodenal contents were made on 21 patients, using collections for one hour before injection following a minimal 6 hour fast as control. Specimens were collected at intervals for one hour after the intravenous injection of 1 mg. per kilo of body weight of "pancreatost" secretin. Patients varied from 6 weeks to 11 years of age, with diagnoses of idiopathic celiac disease, pancreatic fibrosis, chronic nutritional disturbance and selective trypsin deficiency. (Analytical techniques are given by the same authors in *Am. J. Dis. Child.*, 66, 418, October 1943.) No untoward results have been reported from the intravenous use of secretin even with repeated injections in the same individual. Analyses were for volume, pH, color, viscosity, and usually trypsin, amylase and lipase. In normals and all cases except those of pancreatic fibrosis there was a postinjection increase in volume

and pH. Pancreatic fibrosis and trypsin deficiency both failed to show postinjection increase in tryptic activity. All cases except fibrosis showed increase of lipase after secretin, and there was increased amylase in all but fibrosis and celiac disease, in which there was a decrease. The authors point out the value of the test in distinguishing the clinically similar conditions of chronic fibrosis and celiac disease. They suggest, for more complete study, the use of vagal stimulation by mecholyl as well as the humoral stimulation by secretin. The former produces a higher content of enzymes, while the latter appears only to wash out enzymes already formed.—B. C. Riggs.

LIVER AND GALLBLADDER

AMBERG, L.: *Prognosis of chronic hepatitis in children.* (*Proceed. Staff Meet. Mayo Clinic*, V. 18, P. 494, Dec. 15, 1943.)

Chronic hepatitis generally includes cirrhosis of the liver. The histories of 68 cases of chronic hepatitis in children showed that in the younger ages male children predominated. Cases ending in cirrhosis often extended over a period of five years. Chronic hepatitis did not always end in cirrhosis, but sometimes healed. The worse cases were those described as acute yellow atrophy in which diffuse destruction of the liver cells resulted in death before signs of repair developed.—N. N. Underhill.

LUDWIG, H.: *Testing liver function with galactose.* (*Helvetica Med. Acta.*, V. 10, P. 63, 1943.)

As a liver test, 40 grams galactose dissolved in one liter of water are drunk by the patient, and his total galactose secretion and the galactose concentration of the urine determined. If galactose secretion lasts longer than 2 hours, or if the urinary galactose concentration during the first one and a half hours is higher than 0.35 per cent, liver damage is present.—Courtesy Biological Abstract.

GRAHAM, R. L.: *Sudden death in young adults in association with fatty liver.* (*Bull. Johns Hopkins Hospital*, 64:16, January 1944.)

Five cases of sudden death in adults of average age 34.2 years are abstracted; three were white males and two were white females. Chronic alcoholism was definite in three and suspected in the fourth. Heat stroke or exhaustion was ruled out as a cause of death. Examination of the tissues for alcohol gave figures which were too low for acute alcoholism at the time of death. In all these cases only one abnormality of consequence was discovered at autopsy, this being a large liver in which most of the liver cells were packed with yellow fat. In three of the cases no normal liver cells could be found. In some of the cases convulsive seizures similar to epilepsy occurred. Blood sugars were obtained in only one case and in this it was normal. No known reason for the cause of the sudden death has been ascertained, but a vitamin-deficient diet, with or without hypoglycemia, may have been a factor.—William Dale Beamer.

SEPULVEDA, B. AND OSTERBERG, A. E.: *A modified technic for the determination of serum bilirubin: A preliminary report of its clinical use.* (*Arch. Intern. Med.*, V. 72, P. 372-376, 1943.)

A preliminary report of the clinical use of a new technic for the determination of bilirubin in the serum was made. The concentrations of bilirubin of normal persons and patients who did not have hepatic disease ranged from 0.1 to 0.8 mg. per 100 cc of serum. The values for bilirubin were 0.5 mg. or less per 100 cc of serum in 95.5 per cent of these cases. The van den Bergh reaction was indirect in all these cases. Values for bilirubin, giving the indirect van den Bergh reaction, may be slightly elevated in cases of hepatic disease without jaundice in which serum bilirubin giving the direct van den Bergh reaction is not found and apparently may indicate hepatic damage when hemolytic jaundice is excluded. These values may be elevated when the bromsulfalein test of hepatic function does not disclose dysfunction of the liver and apparently may indicate hepatic dysfunction when the bromsulfalein test does not. The concentration of bilirubin giving the indirect van den Bergh reaction is increased in obstructive and intrahepatic jaundice as well as in hemolytic jaundice. The average concentration of bilirubin giving the indirect van den Bergh reaction in the series was 10 mg. per 100 cc of serum and was found in a case of obstructive jaundice, whereas the highest concentration in a case of intrahepatic jaundice was 5 mg. The difference in the height of the concentration of bilirubin giving indirect van den Bergh reaction in obstructive and intrahepatic jaundice is not sufficiently distinctive to aid in the differential diagnosis of these 2 types of jaundice.—Authors.

MORLACK, CARL G. AND HALL, BYRON E.: *Association of cirrhosis, thrombopenia and hemorrhagic tendency.* (*Arch. Intern. Med.*, V. 72, P. 69, 1943.)

Factors other than the concentration of prothrombin may be of significance in explaining the aberrations from normal noted in the mechanism of blood coagulation in cases of severely damaged livers. Significant thrombopenia in cases of hepatic disease may be an important factor in explaining the severe hemorrhagic tendency sometimes encountered. To determine how often this occurred, a series of 30 cases of hepatic cirrhosis was reviewed. In 17.5 per cent of this group of cases it was found that definite thrombopenia was present. Although a definite hemorrhagic tendency was evident in many cases of hepatic cirrhosis regardless of the level of the blood platelets, this tendency to bleed was relatively twice as frequent when thrombopenia was associated. However, a hemorrhagic tendency is not exhibited in all cases of thrombopenia for in 2 of a total of 14 cases of cirrhosis and thrombopenia bleeding of any kind did not occur. The records in 50 cases of splenic anemia were also studied. In splenic anemia the incidence of bleeding was increased correspondingly. In this group, as in that of cirrhosis, a greater tendency to bleed was evident in those cases in which the reduction in the level of thrombocytes was most significant. It is believed that the diminution of

the blood platelets in severe hepatic disease of long standing is not a chance and unimportant finding. The alteration of the level of the blood platelets in these cases was not explained, but it is believed that when this formed blood element is significantly reduced from normal, the bleeding hazard is increased definitely.—Authors.

GORDON, I.: *Infective hepatitis with special reference to the oral hippuric acid test.* (Brit. Med. J. No. 4329: 807, Dec. 25, 1943.)

The clinical features of infective hepatitis in 168 cases in the Middle East Forces are described. Dysentery and diarrhea were associated with the onset in only 9 cases; respiratory infections and sore throats in only 8 cases. The onset was usually sudden with fever ranging from 100° to 102° in 88 cases, but in 80 cases the onset was afebrile, with jaundice the first symptom in 8, slight frontal headache in one-third, and loss of appetite, nausea and vomiting, abdominal pain, constipation, etc., in the rest. Enlargement of the liver was detected in 49 per cent of the cases with febrile onset, and 51 per cent of the cases with afebrile onset. In over two-thirds, the jaundice lasted 15 to 35 days. The leukocyte count was either low or normal, and the differential count was usually normal. The urine showed increased bile and urobilinogen, except for the latter when stools were clay colored. The original test devised by Quick in which 6 grams of benzoic acid are given by mouth and all urine is collected for four hours, was performed in 14 cases during the first 3 weeks of jaundice. Normally 90 per cent of 3 grams will be excreted in the form of hippuric acid in this time. Evidence of impaired function of from 37 to 72 per cent of the normal was found in all. The test was performed in 29 cases when jaundice had almost disappeared, with the result that 19 cases showed liver insufficiency. Ten cases were examined after 2 to 4 weeks of convalescence and no jaundice was present. Of these 10 cases, 4 still showed liver insufficiency by the hippuric acid test. The degree of jaundice or hepatomegaly is not always in constant relationship to the liver function, as estimated by the hippuric acid test.—Wm. D. Beamer.

ULCER

COLLINS, V. P.: *The peptic ulcer and chronic gastritis.* (Ann. Surg., 118: 1005, Dec. 1943.)

Endeavoring to define the meaning of the term "chronic gastritis", the author presents the microscopic appearance of 213 surgically resected stomachs. It was thought that any relationship between chronic gastritis, peptic ulcer and carcinoma would be noted in the epithelial rather than the inflammatory elements. The term chronic gastritis may be applied when degeneration, necrosis and repair occur. When degeneration and necrosis occur with inadequate mechanism of repair, a recognizable peptic ulcer results. The element of repair is an essential part of the process. When the proliferative response is recurrent and prolonged, the germinal epithelium may become exhausted and atrophic gastritis result. The symptomatology of peptic ulcer can be explained on a basis of chronic gastritis

when no ulcer is found, since the ulcer is only the obvious manifestation of chronic gastritis as defined. It is possible that duodenal ulcers are only apparently more frequent than gastric ulcers because the former produce recognizable deformities when minimal. Hypertrophic gastritis is only a descriptive term since the apparent thickening of the mucosa is due to the mechanical effect of edema of the submucosa.—Wm. D. Beamer.

WADE, HENRY J.: *Dyspepsia in the Royal Navy: Study of 1003 consecutive cases.* (Lancet, 243 (6222): P. 636, 1942.)

These cases are discussed in regard to classification, etiology incidence and relation to war service. Of the 1003 patients, 56 per cent presented clinical evidence of ulcers and 47 per cent showed ulcers on X-ray study. Gastric ulcers occurred in 6.7 per cent, duodenal in 40 per cent and anastomotic in 0.5 per cent. A total of 329 men were invalidated—Biological Abstract.

BENNER, M. C.: *Peptic ulcers in infancy and childhood.* (J. Pediat., 23, 463, Oct. 1943.)

The condition of ulcer in childhood though previously disregarded in diagnosis is now receiving more attention. This report presents post-mortem studies of eight cases in which either the active ulcers or the healed lesions were found. The causes of these ulcers were variously regarded as due to vascular accidents at birth, severe infectious diseases of the central nervous system, peritonitis by *Clostridium Welchii*, and possible toxicity of Rhubarb leaves. Several ulcers were found at autopsy which had given rise to no diagnostic symptoms and healed without specific treatment.—G. Clements.

THERAPEUTICS

MAGERL, J. F.: *Gastric hyperacidity and its treatment with potato juice.* (Deutsch. med. Wochschr., 67: 119, Jan. 31, 1941.)

Titration of samples of gastric juice do not reflect the actual acidities accurately as larger volumes may affect the values by dilution. The usual dietary regimen does not really improve ulcers or inflammatory conditions of the stomach associated with hyperacidity. Large volumes of fluid in the stomach are of value in diluting the acid and soothing the mucous membrane. In a series of twenty-five patients, 19 with severe chronic hyperacidity associated with gastritis or ulcer and 6 with acute gastritis, cure of the condition was effected in twenty-two by the ingestion of juice of raw potatoes. The maximum dose was 400 cc per day. The juices given usually for 10 days to 3 weeks. Best results were obtained with red potatoes which contain 3 to 20 mg. per cent of solanin and 16 to 19 per cent of starch. The action is probably complex, with the solanin reducing spasm, producing mucus and overcoming constipation, while the starch and salts buffer the acid. No side effects or toxic reactions were observed.—Wm. D. Beamer.

CRABB, A. J.: *Peptic ulcer, an endocrine disease.* (Kansas Med. Soc. J., V. 44, P. 368, Nov. 1943.)

Crabb expresses the opinion that peptic ulcer is essentially a disease resulting from a deficiency of parathyroid hormone. Placed on this endocrine basis, therapy becomes a matter of substitution. In his hands gratifying results have been obtained with substitution therapy with parathyroid hormone. Treatment commences with single injections every three days and gradually tapers off to injections once every three weeks. Alkaline powders are given before an expected onset of pain but are not permitted after meals. Liquids and soft foods are used exclusively during the first part of the treatment but eventually the diet is enlarged to include a variety of foods.—N. N. Underhill.

CALDWELL, W. A., AND S. W. HARDWICK: *Chronic Flexner dysentery treated with succinylsulfathiazole.* (Lancet, V. 2, P. 544, Oct. 30, 1943.)

A woman had Flexner dysentery for about one and one-half years. Intermittent periods of diarrhea accompanied by positive stools were present during this time. Sulfaguanidine was tried but failed. However, her symptoms disappeared and her stools became negative after succinylsulfathiazole therapy.—F. E. St. George.

SURGERY

BABCOCK, W. W. AND BACON, H. E.: *The elimination of colostomy in the radical treatment of cancer of the large bowel.* (Penn. Med. J., 46, 1143/, Aug. 1943.)

In this article, based on over 400 cases, a plea for the elimination of colostomy is made. Instead of colostomy the authors advise end-to-end anastomosis of the large bowel if the resection for cancer is made above the pelvis, and end-to-perineum anastomosis if the resection is below the pelvis. In the latter procedure, recent studies show that the anal sphincters can usually be saved and reutilized, as the anus and sphincters are not involved by malignancy in 90% of the resection cases due to lymphatic drift of cancer cells away from these parts.

Even when the anus and sphincters are involved and must be removed, an artificial opening in this area is advised. An opening here has proved to be much more satisfactory to the patient than colostomy since a high degree of self control is regained over artificial openings here. In most cases no pads are needed except when diarrhea occurs. This allows patients to regain their self respect, and to hold jobs which frequent, uncontrolled escape of gas from the colostomy previously prevented them from holding.

The article also discusses the methods of performing these operations.—Glenn Clements.

ANDERSON, R.: *Failures in inguinal hernia.* (Canadian Med. Assoc. J., V. 49, P. 392, Nov. 1943.)

University Hospital records at Edmonton show that of every 6.25 hernias repaired one was a failure and that one of every 7 hernias repaired had been a previous failure. Wound discharge was more apt to occur with catgut than with silk sutures in a ratio of 16:3.

The "sac only" technique showed one of the lowest recurrence rates and strongly suggested its superiority over the "Bassini" procedure.

"Fascia lata flap" operations were eminently successful even in repair of recurrent hernias. The hernial sac should not be used as a patch. The techniques of "living transplant suture," "cord superficial," the various "imbrication" methods, "cord buried" and the "Bassini's" with various modifications, are inadequate.

The technique of "transversalis fascia" plus added procedures promise much freedom from recurrence. The anatomy and physiology of the problem is reviewed with conclusions stated. The external oblique and the external ring play little or no part in the etiology of hernia. The whole problem of repair of the inguinal hernia probably centers around the manner in which the posterior wall triangle is dealt. Fasten the first line of defense, the "transversalis fascia" to its own structure and insertion and then patch the outer defense with a pedicle or free patch from fascia. The repair is accomplished by the application of fundamental, well established surgical principles used meticulously and intelligently.—John J. Cox.

CLINE, JOHN W.: *Gastric resection for peptic ulcer.* (California and West. Med., V. 59, P. 7, 1943.)

A series of 83 cases of resection of the stomach for complications is presented and the indications for operation, preoperative preparation, operative procedure, post-operative care and results are discussed. Resection of two-thirds of the stomach including the pylorus and antrum is based upon sound physiological principles and is the operation of choice in most cases of peptic ulcer requiring surgical intervention.—Courtesy Biological Abstracts..

EXPERIMENTAL MEDICINE

SECRETION

ANDRUS, W. DE W., LORD, J. W., SHEFKO, P., AND DIGWALL, J. A., III.: *The effect of saline washings of isolated jejunal loops on gastric secretion.* (Am. J. Physiol., V. 140, P. 287, Dec. 1943.)

Short Thiry loops of the jejunum were prepared in several dogs. The loops were washed out several times with 25 cc of physiological saline and then the saline washings instilled into the stomach of normal dogs. After ten minutes the jejunal washings and the gastric contents were removed from the stomach and histamine given. Control experiments consisted of administering an equal volume of saline instead of saline washings.

A definite fall in both free and total acidities was produced by the washings from the jejunum. This depression in gastric acidity persisted for at least 20 minutes. The authors attribute this effect to a substance within the jejunal loop.—M. H. F. Friedman.

COMFORT, M. W. AND PRIESTLEY, J. T.: *External pancreatic fistula: report of case with physiological observations and surgical considerations.* (Proceed. Staff Meet. Mayo Clinic, V. 18, P. 409, Nov. 3, 1943.)

The paper reports the rare case of a man with an externally draining pancreatic fistula of long standing

which secreted daily approximately 250 cc of clear pancreatic juice. During fasting, the volume of pancreatic juice secreted was low, varying from 0.4 to 3.9 cc per 30 minutes. After oral administration of 100 gm. glucose in 200 cc water, the volume decreased but rose again to reach maximum values during the fourth and fifth hours. Ingestion of 25 gm. casein in 200 cc water resulted in 9.0 cc of juice during the first 30 minutes; the secretory rate remained at this level for two hours. Total bicarbonate, total lipase and total amylase values ran parallel to the volume curve. Since the gastric juice was permitted to enter the duodenum, the pancreatic secretion in response to glucose or casein was similar in character to duodenal instillation of acid or the injection of secretin.

The response of the pancreas to oral administration of 59 cc olive oil and 200 cc water was dissimilar to the response to casein. The secretion diminished during the second 30 minute period and remained low. Bicarbonate and lipase were also low but the secretion of amylase was increased. This was dissimilar to the response to casein because the olive oil probably inhibited gastric secretion or else prolonged gastric emptying time.

The above substances were also introduced directly into the duodenum after continuous aspiration of the gastric contents. In these experiments the glucose and casein resulted in smaller volumes of pancreatic secretion than with the olive oil.

In a third series of experiments it was found that a high carbohydrate, low fat, low protein meal provoked a greater pancreatic secretion than did a high fat, low carbohydrate, low protein meal.—M. H. F. Friedman.

MOTILITY

HADARY, G., SOMMER, H. H., AND GONCE, J.: *The relationship between the curd tension and gastric emptying time of milk in children.* (J. Dairy Sci., V. 26, P. 259, 1943.)

This study was undertaken to investigate the relationship between the curd tension measurement of milk and the rate of elimination of the milk from the stomachs of normal young individuals as indicated by roentgenograms. The course of a control milk having a high curd tension and that of chocolate, homogenized, base exchange, and evaporated milks having low curd tension was followed through the digestive tract of 7 young children with the aid of roentgenograms. From the roentgenograms the percentage of stomach or colonic emptiness was estimated. The records of these estimates were analyzed statistically using an analysis of variance technique. It was concluded that no correlation existed between the curd tension of bariumized milk and stomach or colonic emptying time of children. Soft curd milks did not leave the digestive tract more rapidly than the hard curd milks. Chocolate milk behaved in this respect as did all other soft curd milks.—Courtesy Biological Abstracts.

VAN LIER, EDWARD J., NORTHRUP, DAVID W., STICKNEY, J. CLIFFORD, AND EMERSON, GEORGE A.: *The effect of anoxia on peristalsis of the small and large*

intestine. (Amer. J. Physiol., V. 140, P. 119, 1943.)

By a modified Macht technique, it was found that intestinal motility was significantly decreased during exposure of mice to an oxygen pressure of less than 94 mm. Hg., but that intestinal motility in dogs was affected by oxygen of 80 to 43 mm. Hg. The threshold level of anoxia causing diminution of contractions of both circular and longitudinal muscle of the colon of barbitalized dogs lay between 94 to 110 mm. Hg. pressure. The mode of action of anoxia on intestinal muscle is briefly discussed.—Courtesy Biological Abstracts.

ABSORPTION

Csaky, T.: *The structure of the glucose molecule in relation to resorption from the small intestine.* (Hoppe Seyler's Zeitschr. Physiol. Chem., V. 227, P. 47, 1942.)

The 4 compounds 2-, 3-, 5-, and 6- glucose methyl ethers, were prepared and their absorption by white rats determined. The rats were fasted 24 to 36 hours and then anesthetized. A one centimeter incision was made at the midline of the abdomen and the lower end of the small intestine ligated. A second incision was made in the epigastrium and the duodenum ligated beneath the pylorus. After the injection of 2 to 3 cc of the isotonic sugar solutions into the small intestine, the animals were kept at room temperature for one hour, killed, and the amount of carbohydrate remaining in the small intestine determined. The 3-glucose methyl ether was absorbed as rapidly as glucose, but 2-, 5-, and 6- glucose methyl ethers were absorbed much more slowly. During absorption, the phosphate esters formed seemed to be an equilibrium mixture in which fructose—1-, 6-, diphosphate predominated.—Courtesy Biological Abstracts.

PATHOLOGY

LADIEWIG, PETER.: *Anoxaemic changes in the liver with regard to the "high-altitude death" of airmen.* Nature (London), V. 151, (3837), P. 558, 1943.)

Liver cells of guinea pigs kept in deep chloroform anesthesia 3.5 hours presented the same type of big, round or polyhedral vacuoles as in men dead from effects of high altitude.—Biological Abstract.

METABOLISM AND NUTRITION

KELLY, H. T.: *Appraise vitamin formulas and not titles.* (Pennsylvania Med., V. 46, P. 881, June 1943.)

To evaluate a vitamin combination it is necessary to know the amount of the vitamins it contains. For this reason their biologic activity should be expressed in terms of a common system and where possible the weights, in grams, of the vitamins should be given. The vitamins should be present in the ratio of the adult minimum daily requirement to permit adequate dosage of any component without waste of others. Five times the daily recommended allowances or maintenance levels should be prescribed for therapeutic doses. It is also necessary to bear in mind the cost of the product on the basis of the daily cost of supplying the therapeutic requirements of the individual.—H. T. Kelly.

Endometriosis of The Rectosigmoid

*Report of a Case with a Review of the Literature**

By

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ALTHOUGH many instances of endometriosis of the rectosigmoid have recently been reported in the literature, the majority of the cases were found during routine gynecological operations. The diagnostic features of the condition have not been sufficiently stressed nor is there adequate data in the literature describing the roentgenographic features of the disease. It would therefore seem worth while to review the literature with a description of a case illustrating the X-ray appearance upon which the diagnosis was made.

The term endometriosis denotes the migration of endometrial tissue outside the uterine cavity. These endometrial implants may invade the adjacent structures as well as any portion of the gastrointestinal tract, inguinal region, or the umbilicus.

Incidence

Endometriosis of the reproductive organs is now recognized as a fairly common disease. Thus in 1,000 gynecological surgical cases, Green-Armytage¹ found endometriosis in 8.9%. It occurs most often between the age of 30 and the menopause, although it is known to have occurred at the ages of 18 and 67.

The incidence of endometriosis involving the rectosigmoid is difficult to determine. It is possible that it occurs more often than is indicated in the literature, since, before marked symptoms appear, many patients may reach the menopause, at which time the disease disappears spontaneously. Jenkinson and Brown² found endometriosis of the rectosigmoid in 47 of 117 cases or in 40%. Allen³ found endometriosis of the bowel in 41 of 112 patients or in 37%. Cattel⁴, in his series of 104, found that 17 cases, or 16%, had involvement of the rectosigmoid. Counsellor⁵ reported 162 cases with 51, or 31%, involving the rectosigmoid and rectovaginal septum. Keene and Kimbrough⁶, in 118 cases, found only 6 involving the rectosigmoid.

About 50% of the cases of endometriosis of the large bowel had some degree of intestinal obstruction. Thus there was obstruction in 21 out of 47 cases reported by Jenkinson and Brown², in 12 out of 17 cases reported by Cattel⁴, and in 15 out of the 38 cases reported by Mayo and Miller⁷.

Pathology

It is characterized by diffuse or multiple areas of ectopic endometrium-like tissue, consisting of characteristic glands, stroma and occasional smooth muscle. These tumors consist of tall columnar cells, surrounded either by the typical round cell stroma or smooth muscle fibers. Metastatic implants may occur anywhere in the gastrointestinal tract. Thus involvement of the

colon, small intestines, appendix, inguinal region, and umbilicus have been described. The implants usually occur on the serosal layers with subsequent involvement of the muscular coats. The mucosa is rarely involved.

There are many theories as to the origin of endometriosis. Thus Chiari⁸ believed that it is inflammatory in nature. Another theory is that Muellerian or Wolfian cell rests are stimulated to proliferation in adult life. Sampson⁹ believes that the endometrium shed from the uterine canal at the time of menstruation is forced through the fimbria of the Fallopian tubes and becomes implanted on the peritoneum. Another widely held theory is that an inflammatory irritation of pluro-potential serosal cells produces metaplasia to endometrium-like tissue.

Diagnosis

The symptoms of endometriosis of the rectosigmoid is that of pelvic endometriosis in addition to gastrointestinal complaints. As stated before, it occurs most often between the age of 30 and the menopause, although it is known to have occurred at the ages of 18 and 67. Sterility, dysmenorrhea of the acquired type, metrorrhagia and menorrhagia are common.

When the rectum or sigmoid is involved, there may be abdominal distention, flatulence and vague abdominal pain. There may be cramps, constipation or diarrhea and pain on defecation. All these symptoms are usually aggravated before and during the menstrual period. In some cases there are symptoms of partial or complete intestinal obstruction. Physical examination is usually negative except for the pelvic lesion. The distinguishing feature between endometriosis and carcinoma of the rectosigmoid is that in the former the general condition of the patient is good. There is no weight loss, there is usually no occult blood in the stool, and the history is of longer duration. Sigmoidoscopic examination may reveal narrowing of the lumen of the bowel with intact but puckered mucous membrane. The mucosa is rarely involved and a biopsy is usually negative.

Roentgenologic Features of Endometriosis of the Rectosigmoid

There is very little in the medical literature describing the X-ray characteristic of endometriosis of the rectosigmoid. Thus Mayo and Miller⁷ state there are no roentgenographic peculiarities for endometrioma of the bowels. Maclean¹⁰ states the barium enema contributes but little evidence to the diagnosis, as the tumor produces no obvious filling defect on the film. Jenkinson and Brown² state that the characteristic lesion is a long inconstant filling defect with sharp regular bor-

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ders, intact mucosa, and fixation of the bowel which is very tender to palpation. In the case reported here, the filling defect was constant, the borders were regular and sharply demarcated, the mucosa was puckered and



Figure 1—Barium enema roentgenogram showing a filling defect in the rectosigmoid with intact mucous membrane.

intact. The demonstration of an intact mucosa by X-ray differentiates this condition from carcinoma.

Treatment

Castration, either surgically or by deep X-ray therapy, will cause the lesion to disappear. Maclean¹⁰ believes that X-ray treatment should be the method of choice in a woman near the end or past the child-bearing age. In a young woman, because of conservation of the child-bearing function and avoidance of the troublesome symptoms of an acute menopause, surgical removal of tumor is indicated. Cattel¹ states that if the rectoraginal involvement is extensive and is producing a severe obstruction, a bilateral oophorectomy is indicated with or without a colostomy. Colostomy, if performed, is temporary and can be closed in a few months. In all cases, roentgen examinations of the colon by barium enema should be made following sterilization. Two months following castration, the lumen of the bowel should be restored.

Report of Case

F. R., female, married, age 37, was admitted to the hospital October 16, 1940, complaining of a mass in the lower abdomen and of lower abdominal pain.

About ten months prior to entry, the patient had an attack of pain in the lower abdomen, associated with diarrhea. The pain and diarrhea lasted about two days and then disappeared. It then recurred periodically. She stated that the attacks were worse during the men-

strual period. In the intervals there was obstipation associated with ribbon-like stool. She did not observe any blood in the stool. Her appetite was good and there was no loss of weight. Three months before admission she noticed a large mass in the lower abdomen which had progressively increased in size. For the past four months she had metrorrhagia and dysmenorrhea.

Her family history was non-contributory. She was married at the age of 21, with one pregnancy resulting. The age of the child was 13 years. No other pregnancy took place.

Physical examination revealed a well nourished female somewhat distressed. The skin and mucous membranes were normal. The tongue was coated but moist. The heart was not enlarged, the sounds at the apex and base were normal. No murmurs were heard. The lungs were normal. The abdomen was slightly distended. The liver and spleen were not felt. A large firm mass was felt in the lower abdomen. It extended midway between the umbilicus and the symphysis pubis. It was fixed and not tender. There was no edema of the extremities. The reflexes were normal. Vaginal examination disclosed an erosion of the cervix. The mass was felt bimanually and was not movable. Manipulation caused pain. Temp. 98.6; P. 90; R. 18; B.P. 130/80.

Laboratory

The urine was normal. Blood count showed R.B.C. 4,640,000; Hg. 90%; W.B.C. 8,000. Differential count: band forms 4, segmented forms 60, small lymphs 26, monos 4.



Figure 2—Oblique view roentgenogram demonstrating a constricting lesion.

On sigmoidoscopic examination, the instrument passed easily for a distance of about six inches, beyond which it met with an obstruction. No tumour masses were seen and the mucous membrane was normal.

A flat plate of the abdomen did not reveal any abnormalities. An examination of the colon by means of a barium enema showed a constant filling defect in the region of the sigmoid (Fig. 1). The mucosa appeared puckered but intact. An oblique view showed a constriction in that area, with regular borders (Fig. 2).

An operation was performed on October 19. There was a fibroid uterus larger than a grapefruit. The right ovary was three times the normal size. Both tubes and ovaries were bound down by multiple, firm, dense adhesions. The rectum was adherent to the left tube and uterus. On the anterior wall of the sigmoid a hard firm tumor mass was felt. This mass occupied almost the entire circumference of the bowel and extended to about an inch and one-half in length. Proximal to the tumor the bowel was slightly dilated. The uterus and both tubes and ovaries were removed. It was felt that the tumor in the sigmoid was caused by endometriosis, and it was therefore not removed.

Pathological examination showed that the large cyst in the right ovary was lined by columnar epithelium which lay upon tissue of endometrial stroma character in some places, and in others, upon a loose cellular tissue containing numerous histiocytes filled with brown pigment. Glands of endometrial character were present within the mesentery of the ovary. These involved the serosal aspect of the meso-ovarium. Diagnosis: endometrial cyst of ovary. Endometriosis of mesoovarium.

The patient made an uneventful recovery and was discharged on November 3, 1940. Sigmoidoscopic examination six months later showed the sigmoid to be patent and a normal mucous membrane. A barium enema X-ray of the colon did not show any filling defect in the sigmoid (Fig. 3). At this writing, three years after the castration, the patient is well and has gained 24 pounds in weight.

Comment

The patient's history of sterility, menstrual disorders, abdominal symptoms aggravated during the men-

strual period, plus sigmoidoscopic and X-ray examination of the colon, were sufficient to make a diagnosis of endometriosis of the bowel. The distinguishing features of the roentgenogram were a constant filling defect in



Figure 3—Barium enema roentgenogram 6 months after castration, showing disappearance of filling defect.

the rectosigmoid with an intact but puckered mucosa. Resection of the tumor was not necessary and castration caused a disappearance of the lesion.

Summary

The clinical course of endometriosis of the sigmoid is described with a review of the literature. A case is presented illustrating the roentgenographic features of the disease and stressing the importance of differentiating it from carcinoma.

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The Direct Van Den Bergh Reaction in Mixtures of Normal and Jaundiced Serum

By

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THE method of Malloy and Evelyn¹ for the quantitative estimation of serum bilirubin has renewed interest in the possible clinical significance of determinations of direct bilirubin in the serum²⁻⁵. With this procedure, all of the serum bilirubin reacts in 30 minutes with the van den Bergh reagent in acid 50% methyl alcohol (indirect reaction), whereas a variable fraction reacts in aqueous acid (direct reaction). The magnitude of this fraction varies in normal serum and in the serum of subjects with various types of jaundice⁶. The nature of the difference in the fractions of bilirubin responsible for this difference in reaction is not definitely known^{4,5,6,7}. In the past, considerable attention was directed to the possibility that an increase in the concentration of surface-active substances (bile salts, cholesterol, fatty acids) in the serum may be responsible for the production of the direct reaction. However, the demonstration of the presence of a considerable, but variable quantity of "direct-reacting" bilirubin in normal serum simultaneously with a non direct-reacting fraction suggests that the essential difference lies either in (a) the bilirubin molecule or its mode of combination in the serum or (b) in other agents in the serum that catalyze or inhibit the direct reaction (aqueous acid). The present study was undertaken for the purpose of investigating the effect upon the quantity of "direct" bilirubin of mixing sera containing widely differing concentrations of total bilirubin and protein and varying concentrations and proportions of direct-reacting bilirubin.

Material and Methods. Determinations of total and "direct" bilirubin were made upon the following materials: (1) 8 samples of serum from patients with obstructive jaundice; (2) serum of a patient with congenital hemolytic jaundice; (3) serum of a patient with obstructive jaundice concentrated by ultrafiltration (cellogelmembranes); (4) serum of a patient with congenital hemolytic jaundice, concentrated by ultrafiltration; (5) serum of normal subjects and (6) water solutions of dried normal plasma (Lyovac) approximating 20% of the concentration of solids in normal plasma. These samples were placed in varying proportions, as indicated in the tables, and determinations of total and "direct" bilirubin were made after the mixtures had stood at room temperature for 30 minutes. All determinations were made by the method of Malloy and Evelyn¹, the "direct" readings being made at 10 and 30 minutes. The observed (30 minute) direct bilirubin values were compared with the theoretical values calculated on the basis of the percentages present in the original samples.

Results and Discussion. The results are presented in Tables 1-7, and may be summarized as follows:

(1) When serum of either obstructive or hemolytic jaundice was subjected to ultrafiltration, with a consequent proportional increase in albumin, globulin and bilirubin, there was no alteration in the proportion of "direct" bilirubin. The ultrafiltrate contained no demonstrable bilirubin, in agreement with the observations of Gregory and Andersch⁸ and Coolidge⁷.

(2) When serum of obstructive jaundice was mixed with concentrated normal plasma (Exp. 4-6, Table 1) in proportions of 4:1 to 1:5, with consequent simultaneously increasing protein and decreasing bilirubin concentrations, there was a consistent difference between the actual and theoretical concentrations and proportions of direct bilirubin. With diminishing bilirubinemia, at total protein concentrations below 10% and albumin concentrations below 7%, the actual percentage of direct bilirubin slightly exceeded the theoretical. With further fall in total bilirubin and increase in protein above these levels, the actual percentage of direct bilirubin fell progressively below the theoretical.

(3) When serum of hemolytic jaundice was mixed with concentrated normal plasma (Exp. 9, Table 4), in proportions of 4:1 to 1:4, the findings were practically the reverse of those obtained with serum of obstructive jaundice; i.e., with diminishing bilirubinemia and increasing proteinemia (above 8%), the actual proportion of direct bilirubin increased progressively above the theoretical.

(4) When obstructive jaundice serum was mixed with normal serum in a proportion of 1:2 (Exp. 7, Table 2), with only slight change in protein concentration and decrease in bilirubin, the actual proportion of direct bilirubin fell below the theoretical.

(5) When hemolytic jaundice serum was mixed with normal serum (Exp. 10, Table 5), in proportions of 4:1 and 1:1, with no change in protein and decreasing bilirubinemia, the actual proportion of direct bilirubin increased progressively above the theoretical.

(6) When serum of obstructive and of hemolytic jaundice were mixed in equal proportions (Exp. 12, 13, Table 7), the actual proportion of direct bilirubin was greater than the theoretical.

Data reported by Coolidge⁷ led him to conclude that all of the bilirubin in human plasma with a high bilirubin content is bound to albumin, that passing a direct reaction in 10 minutes (Malloy and Evelyn's test) attached to albumin as a disaccharide complex with the use of concentrated protein as adsorbent, 1 cc. of 2% solution of orange solution of albumin adsorbed 1.5 cc. of 1% solution of 72.5% bilirubin solution.

Obstructive Jaundice. Serum mixed with concentrated normal plasma. Increasing protein concentration and decreasing bilirubin concentration.

Oxysterol Analyses. Serum mixed with concentrated normal plasma, saturated with oxysterol.															
Exp.	Sample	Protein		Total	Albumin, mg. per 100 cc.		Direct		10 minutes		30 minutes		Difference		
		Alb.	Glob.		actual	calculated	actual	calculated	actual	calculated	actual	calculated	10 minutes	30 minutes	
1	Serum	3.8	2.7	6.5	20.6	14.6	16.1	71	71	78	78				
	Concentrate	8.6	4.0	12.6	1.4	0.15					14				
	S:C—2:1	5.4	3.2	8.6	14.2	10.1	9.77	11.5	10.78	69	81	76	76	+2	+3
2	S:C—1:4	7.0	3.8	11.7	5.2	2.2	3.04	2.6	3.35	58	50	64	64	+16	+14
	Serum	3.2	2.5	5.7	24.4	16.6	17.4	68	68	71					
	Concentrate	9.6	3.8	13.4	1.7	0.1				6	12				
3	S:C—1:1	6.4	3.2	9.6	13.1	8.9	8.35	9.0	8.8	64	67	67	67	+4	+2
	S:C—1:2	7.5	5.1	12.6	9.3	5.0	5.6	5.1	5.9	60	55	63	63	+6	+8
	Serum	3.1	2.8	5.9	22.5	16.5	18.5	73	73	82					
4	Concentrate	9.4	3.7	13.1	1.5	0.2				13	17				
	S:C—4:1	4.3	3.0	7.3	18.3	13.9	13.2	15.7	14.8	76	86	81	81	+4	+5
	S:C—1:4	8.2	3.6	11.8	5.7	2.9	3.5	3.2	3.9	51	57	68	68	+10	+11
5	Serum	4.2	2.1	6.3	18.3	12.8	13.9	13.9	13.9	70	76				
	Concentrate	9.4	3.7	13.1	1.5	0.2				13	17				
	S:C—4:1	5.2	2.4	7.6	14.9	10.8	10.3	11.6	11.2	72	78	75	75	+3	+3
6	S:C—3:1	5.5	2.5	8.0	14.1	10.0	9.6	11.0	10.5	71	78	74	74	+3	+4
	S:C—2:1	5.9	2.6	8.5	12.7	9.2	8.6	10.0	9.3	68	79	73	73	+0	+6
	S:C—1:1	6.8	2.9	9.7	9.9	6.8	6.5	7.4	7.1	69	75	72	72	+3	+3
7	S:C—1:2	7.7	3.2	10.9	7.1	4.2	4.1	4.5	4.8	59	63	68	68	+3	+8
	S:C—1:3	8.1	3.3	11.4	5.7	2.8	3.3	3.2	3.7	50	57	65	65	+7	+15
	S:C—1:4	8.4	3.4	11.8	4.9	2.1	2.9	2.3	3.0	43	47	58	58	+12	+19
8	S:C—1:5	8.6	3.5	12.1	4.3	0.9	2.3	1.7	2.5	27	39	38	38	+17	+19
	Serum	4.1	2.8	6.9	16.9	8.8	9.6	9.6	9.6	52	57				
	Concentrate	8.2	3.8	12.0	0.44	0.22				50	68				
9	S:C—2:1	5.5	3.1	8.6	11.4	6.3	6.0	7.3	6.5	55	52	57	57	+3	+7
	S:C—1:1	6.1	3.3	9.4	8.7	4.2	4.5	5.1	4.9	49	52	58	58	+3	+1
	S:C—1:4	7.4	3.6	11.0	3.7	1.4	1.9	1.7	2.1	39	46	58	58	+14	+12
10	Serum	3.9	3.1	7.0	16.7	8.7	10.6	10.6	10.6	52	64				
	Concentrate	9.2	3.6	12.8	1.6	0.35				22	31				
	S:C—4:1	5.0	3.2	8.2	13.7	8.4	7.0	9.9	8.6	61	72	63	63	+10	+9
11	S:C—1:1	6.5	3.3	9.8	9.1	5.2	4.5	6.2	5.5	57	68	61	61	+7	+7
	S:C—1:4	8.1	3.5	11.6	4.6	1.7	2.0	2.0	2.5	37	44	54	54	+6	+10

Obstructive jaundice serum mixed with normal serum. Constant protein concentration and decreasing bilirubin concentration

Exp.	Sample	Protein			Bilirubin mg. per 100 cc.						% Direct		% Difference	
		Alb %	Glob. %	Total %	Direct 10 minutes		Direct 30 minutes		10 minutes		30 minutes		10 minutes calculated	30 minutes calculated
					actual	calculated	actual	calculated	actual	calculated	actual	calculated		
7	Serum A	3.7	3.0	6.7										
	Serum B	4.6	1.8	6.4										
	A:B — 1:2	4.3	2.2	6.5										
					7.6	8.5	0.1	0.2	2.5	2.5	48	54	54	— 9

fate at pH 6.8. On the basis of a single experiment employing mixtures of equal volumes of two plasmas of different bilirubin content, with different proportions of direct-reacting bilirubin, Coolidge⁷ concluded that the differences in reactivity of direct- and non direct-reacting bilirubin are dependent on structural rather than catalytic factors. However, as also pointed out by Castex, Lopez Garcia and Zelaseco⁹, the quantities of direct-reacting bilirubin in these samples of serum was practically identical, a fact which may have been responsible for the failure to obtain a significant difference between the actual and theoretical proportions of direct-reacting bilirubin in the mixture. The latter authors⁹ studied mixtures of equal parts of serum from (a) patients with obstructive jaundice, (b) a normal subject and one with "hepatosis", (c) patients with "hepatosis" and (d) a patient with obstructive and one with hemolytic jaundice. They found that the actual proportion of direct-reacting bilirubin was distinctly higher than the theoretical in each instance except in the case of the mixture of samples from two patients with "hepatosis".

The data reported here suggest that whether or not there is a structural difference between direct-reacting and non direct-reacting forms of bilirubin, the capacity

of the former for reacting with the van den Bergh reagent in aqueous acid depends to some extent upon other factors in the serum. Although the quantity of albumin may be significant in this connection, similar changes were observed in the presence of varying and constant albumin concentrations in the case of both obstructive and hemolytic jaundice serum.

Summary

When samples of serum from patients with obstructive and hemolytic jaundice are mixed in varying proportions with one another or with normal serum or concentrated normal plasma, the actual proportion of direct-reacting bilirubin in the mixture does not coincide with the theoretical, calculated from the quantities present in the components of the mixture. With decreasing bilirubinemia in such mixtures, the actual rose progressively above the theoretical in the case of hemolytic jaundice serum and fell progressively below the latter in the case of obstructive jaundice serum. These findings suggest that the capacity of serum bilirubin for reacting with the van den Bergh reagent in aqueous acid is dependent, in part at least, on factors in the serum other than the bilirubin molecule or the nature of its combination with albumin.

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The Role of The Fat Soluble Vitamins A and D in Nutrition

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(Continued from April Issue)

THE ROLE OF THE LIVER IN VITAMIN A

HOW effective the storage of vitamin A may be in supplying the needs of the animal during periods of depletion is indicated by the work of Davies and Moore (*Davies, A. W. and Moore, T. Vitamin A and Carotene, The Influence of the Vitamin A Reserve on the Length of the Depletion Period in the Young Rat. Biochem. J.* 31:172, 1937.) They showed that in the rat fed with halibut liver oil as a source of vitamin A yielding high reserves of the vitamin, weight increase would continue for several months after stop-

ping its administration. In those rats having a low reserve of vitamin A, growth ceased at the end of five weeks, after such depletion.

The amount of vitamin A stored in the liver is less at birth than in the adult (*Ellison, J. B. and Moore, Thomas. Vitamin A and Carotene: The Vitamin A Reserves of Human Infant and Child in Health and Disease, Biochem. J.* 31:165, Jan., 1937). Ellison and Moore examined the livers of about two hundred children under fifteen years of age at autopsy, that had

died either as a result of accident or disease. Their results confirmed the work of other observers that the vitamin A reserves in young infants were very low. The amount of vitamin A in the liver increased with age and is affected by the vitamin A content in the diet.

The importance of possessing an ample reserve of vitamin A above the actual requirements of ordinary health is also suggested by the work of Moore (*Moore, Thomas. Vitamin A and Carotene. The Vitamin A Reserve of the Adult Human Being in Health and Disease. Biochem. J. 31:155, Jan., 1937*). He obtained 1,000 specimens of livers from patients who died of all types of diseases and the vitamin A content was determined by the antimony trichloride method. For a determination of the vitamin A reserve of the normal adult, those livers were studied of patients who died as a result of accident and not of disease. The median average was 220 International Units per gm.

The typical human reserve of vitamin A based on the physiological requirements of the rat is sufficient to support life for about six months. He found low reserves of vitamin A in individuals who died of septic diseases and he believed that such vitamin A deficiency might be a predisposing cause in some cases in the development of infection. This confirmed the work of Wolff who found subnormal reserves in erysipelas, phlegmons, sepsis and chronic suppurations. Moore also found low reserves in patients dying of chronic nephritis. The vitamin A reserve in these individuals was sufficient for only three weeks as compared with the reserve in the healthy subject which was sufficient for six months.

His work also supported the observations of Wolff that very low reserves, often none at all, were found in the presence of cirrhosis of the liver. The low reserves found in some cases of cirrhosis of the liver is evidently a result and not a cause of the liver injury. In the presence of a failing myocardium, disturbance of the liver because of congestion may be considered as a cause of the low vitamin A reserve.

In puerperal infection, the failure of the liver to store vitamin A occurred even when these patients were treated with large amounts of vitamin A concentrate. Also in cases of chronic nephritis with low vitamin A in the liver, there was nevertheless a preponderance of unconverted carotene suggesting also that there was an impairment in the ability of the liver to convert the carotene into vitamin A. In a significant proportion of cases, however, vitamin A deficiency appeared to be a contributory factor in the susceptibility to the development of infectious disease.

The role of the liver as the great storehouse of vitamin A has been demonstrated experimentally in many ways. As the result of such storage, the organism may be furnished with an ample supply of vitamin A during periods of depletion.

It is an important fact that the body is able to store a sufficient amount of vitamin A to meet its nutritional needs for a long time. This storage potentiality thus provides a great factor of safety during periods of vitamin A depletion, and during periods of shortage, the organism may not readily exhibit obvious organic de-

rangements. The subclinical state of vitamin A deficiency may continue for a long time before physical changes eventually become apparent.

The importance of the liver as a storehouse for vitamin A in the rat is shown by the fact that excluding the fat and skin of the animal, ninety percent of the vitamin A is to be found in the liver. It contains about 200 to 400 times the amount of the vitamin as compared with muscle tissue. On the basis of feeding experiments with fresh skeletal muscle, kidney, lung and liver tissue of rats as a source of vitamin A in the maintenance of the growth curve of the experimental rat. Sherman and Boynton found that the liver was forty times as rich in vitamin A as the muscle (*Sherman, H. C. and Boynton, L. C. Quantitative Experiments Upon the Occurrence and Distribution of Vitamin A in the Body, and the Influence of the Food. J. Am. Chem. Soc. 47:1646-1653, 1925*). When a larger amount of vitamin A was included in the diet of the rat, the concentration of vitamin A was increased four to ten times.

Baumann, Riising and Steenbock (*Baumann, C. A., Riising, B. M. and Steenbock, H. The Absorption and Storage of Vitamin A in the Rat. J. Biol. Chem. 107:705-715, 1934*) showed that about 95% of the total vitamin A was stored in the liver of the rat. Small amounts were also found in the kidneys and lungs. None was found in the brain, blood, muscle or in the alimentary tract. However, when the vitamin A of the liver was absent none of the vitamin was found in any other tissues. The stores of vitamin A in the newborn were very low. This amount gradually decreased until the third week following which there was a rapidly increased storage. The daily addition of six drops of halibut liver oil to female rats during the last five days of pregnancy caused a tremendous increase of vitamin A in the liver. When the liver of the newborn was examined there was also a considerable increase in the amount of stored vitamin A as compared with the newborn in the case where the mother had not received this additional amount of vitamin A.

When the lactating mother was fed an increased amount of vitamin A in the form of halibut liver oil, there was also an increase in the vitamin A of the liver of the suckling. Only a percentage of the vitamin A is absorbed, this varying between 15 to 70% on the basis of the observations of various works (*Davies and Moore 15%; McCoord and Luce-Clausen 25 to 70%*). Baumann, Riising and Steenbock noted that 20% of the ingested vitamin A was recovered in the liver. There is therefore considerable loss of ingested vitamin A. Fecal excretion accounted for only a small portion of this loss. Much of the vitamin A ingested is actually destroyed within the alimentary tract.

Further evidence of the importance of the liver in vitamin A storage is shown by the fact that this process is seriously affected in the presence of liver disease. Greaves and Schmidt (*Greaves, J. D. and Schmidt, C. L. A. On Absorption and Utilization of Carotene and Vitamin A in Cholecholecystostomized Vitamin A Deficient Rats. Am. J. Physiol. 111:192, 1935*) (*Greaves, J. D. and Schmidt, C. L. A. The Utilization*

of Carotene By Jaundiced and Phosphorus Treated Vitamin A Deficient Rats. *Am. J. Physiol.* 111:502, 1935) in 1935 showed that although vitamin A could be absorbed from the intestine of the jaundiced rat deficient in vitamin A, when given orally, nearly all of these rats failed to respond when carotene was administered instead of vitamin A. These experiments indicated the inability of the animal to convert carotene to vitamin A in the presence of jaundice. The jaundice had been produced experimentally by ligating and sectioning the common bile duct.

They also produced liver damage through the administration of phosphorus to rats which had been kept on a vitamin A deficient diet for six to seven days. The ability of the animal to transform carotene to vitamin A was diminished in the presence of the liver disease which had been produced by the phosphorus. The experimental work further emphasized the importance of the normal liver as the organ in which the transformation of carotene into vitamin A mainly occurs.

Haig, Hecht and Patek (*Haig, C.; Hecht, S. and Patch, A. J., Jr.: Vitamin A and Rod-cone Dark Adaptation in Cirrhosis of the Liver, Science* 87:534, 1938) showed that patients with cirrhosis of the liver were susceptible to the development of poor dark adaptation. These patients could be aided materially in recovery from this condition through the administration of large doses of vitamin A. This is evidently due to the inability of the cirrhotic liver to properly convert the carotenoids into vitamin A. This would therefore be an added reason for the inclusion of vitamin A, itself, such as is present in fish liver oils, in preference to the provitamins usually present in the ordinary diet. A disturbed dark adaptation has also been noted in individuals on limited diets over long periods of time in the treatment of peptic ulcer or gall-bladder disease. The inclusion of a vitamin A concentrate should therefore be a valuable addition to the therapy.

The effect of liver pathology on the ability of the liver to store vitamin A is shown in the studies of Haig and Post. (*Haig, C. and Post, J. Vitamin A Concentration in Rat Liver During Recovery from CC14 Cirrhosis. Proc. Soc. Exper. Biol. and Med.* 48:710, Dec., 1941). Carbon tetrachloride was administered to nineteen rats over a period of two months in order to render the liver cirrhotic. There was a definite diminution in the vitamin A concentration of these livers as compared with the livers of a controlled group of rats. This inability of the livers of the animals that had been subjected to the administration of carbon tetrachloride to concentrate vitamin A normally was all the more remarkable since the examination of the livers was made three months after cessation of the poison. In spite of the fact that the histologic changes in the livers were of a minimal character there was nevertheless marked interference with the ability of these livers to maintain a normal reserve of vitamin A.

Ralli, Bauman and Roberts (*Ralli, E. P., Bauman, E. and Roberts, L. B. The Plasma Levels of Vitamin A After the Ingestion of Standard Doses: Studies in*

Normal Subjects and Patients with Cirrhosis of the Liver. J. Clin. Investigation 20:709-713, Nov., 1941) administered 100,000 U.S.P. units of vitamin A to five patients with cirrhosis of the liver and one case of acute catarrhal jaundice. The rise in the plasma level of vitamin A was much less in these patients than in a group of normal individuals to whom a similar amount had been administered.

One patient with cirrhosis of the liver was fed 300,000 U.S.P. units of vitamin A daily. Following this the plasma level of the vitamin increased from 40 U.S.P. units per hundred cc. to 118 U.S.P. units per hundred cc. at the end of three days. The presence of a low plasma level of vitamin A in individuals with cirrhosis of the liver confirms the observation that there is a lowered concentration of vitamin A in the livers of such patients.

Vitamin A was never detected in the urine of normal human beings even when fed with large amounts of the vitamin, nor was it ever found during pregnancy. However in some diseases such as pneumonia and chronic nephritis, vitamin A was found in the urine. In pneumonia the daily excretion of the vitamin in the urine at times amounted to 3,000 International Units. It is in pneumonia and chronic nephritis, the two diseases in which there may be a large output of vitamin A in the urine, that the liver, at autopsy, shows a low reserve of vitamin A (*Lawrie, N. R., Moore, T. and Rajagopal, K. R. Excretion of Vitamin A in Urine. Biochem. J.* 35:825-836, 1941).

Popper and Steigmann (*Popper, Hans and Steigmann, Frederiek. Causes of Drop of Plasma Vitamin A Level in Liver Disease. Proceedings of the Central Society for Medical Research. J. A. M. A.* 121:1413, April 24, 1943) found that the plasma vitamin A levels were zero in almost all cases of cirrhosis of the liver associated with jaundice as determined by means of the examination of specimens of liver obtained by biopsy and examined chemically as well as by fluorescence microscopy. Similar values were found in sixty-six percent of the cases of hepatitis, secondary to malignant obstructive jaundice. In some cases a zero level of vitamin A was found in cirrhosis of the liver unassociated with jaundice, in cases of acute hepatitis as well as in secondary hepatitis with incomplete obstruction. The reduced levels of vitamin A in the blood were apparently the result of impaired liver function.

THE RESULTS OF DEFICIENCY OF VITAMIN A

Eye Disease

IN ADDITION to the stimulation of growth which is a nonspecific characteristic of vitamin A, it has an important function in relation to the maintenance of normal vision; and one of the earliest manifestations of its absence is the development of night blindness.

The relation of vitamin A to visual function is a subject of considerable importance. The pigments in the retina of the eye are present in the rods and cones. The pigment in the rods is known as visual purple or rhodopsin. The pigment in the cones is known as vis-

ual violet. The important fact as regards vitamin A is that it is present in both these pigments. When rays of light reach the retina, the visual purple is bleached, the rhodopsin being altered to a yellowish material known as retinene. The retinene then stimulates the optic nerve and the brain records the visual image.

In order for vision to continue, retinene must be changed back to the original visual purple or rhodopsin. For this conversion to take place vitamin A is essential. Vitamin A is also essential for the regeneration of the visual violet present in the cone. (Hick, S. and Mandelbaum, J. *Relation Between Vitamin A and Dark Adaptation*. *J. A. M. A.* 112:1910, 1929). From this description the significance of vitamin A for the maintenance of visual acuity can be readily understood. A deficiency of vitamin A will interfere with the rapidity with which retinene or visual yellow can be reconverted into rhodopsin or visual purple. Under such circumstances there would be a definite lag in the adaptability of the eye over exposed to light to the reestablishment of its visual acuity. A deficiency in the amount of vitamin A by disturbing the maximum integrity of the visual purple will also reduce the effectiveness of vision when light is dim and ultimately lead to complete night blindness.

The close relationship of vitamin A to the retina is shown by Yudkin, Kriss and Smith (Yudkin, J. M., Kriss, Max and Smith, J. H. *Vitamin A Potency of Retinal Tissue*. *Am. J. Physiol.* 97:611, July, 1931). They extracted the fat from the retina and showed this to be very rich in vitamin A. They obtained pigs eyes from the slaughter house and these were freed from all recognizable surrounding fat. After discarding the fluids in the eye, the retinæ were removed, dried and ground in a mortar. About 1 gm. of the dried retinæ was obtained from one hundred eyes. The arsenic trichloride test was strongly positive. After signs of ophthalmia were obtained in rats on a vitamin A free diet, they were fed weighed quantities of the retinæ. The dried retina proved to be a potent source of vitamin A as indicated by the fact that the eyes were restored to normal within a comparatively short time. When fifty mgm. of the dried retinæ was fed to the animals, the ocular symptoms disappeared in three to seven days. When thirty mgm. of the substance was administered, evidence of eye disease disappeared in five to eleven days. Normal growth was restored and

no evidence of the changes produced by vitamin A deficiency were found at autopsy.

This work confirmed the findings of Holm (1929) who experimented with the retinæ of calves.

The close interdependence of the formation of visual purple on the presence of vitamin A has been definitely demonstrated by Wald (Wald, George. *Vitamin A in Eye Tissues*. *J. Gen. Physiol.* 18:905, July, 1925) indicating that vitamin A is directly involved in the chemical synthesis of visual purple. Although Holm in 1929 and as described above, Yudkin, Kriss and Smith had shown that animals suffering from avitaminosis A could be cured by the addition of material obtained from the retina, it did not necessarily prove that the substance was actually vitamin A, since the carotene might have yielded a similar result. Even the blue color obtained when ether extracts of the pig retina are treated with arsenic trichloride, is not an indication that the substance responsible for the reaction is vitamin A since this may occur with carotened pigments. Based on the fact that the absorption band of vitamin A is different from any natural carotenoid, it was possible for Wald to show that extracts of the retinal and pigment layers obtained from the eyes of frogs, sheep, pigs and cattle, were actually vitamin A and not one of the natural carotenoids. The spectrogram of the anionomic trichloride reaction obtained with an extract of the retina of the ox was compared with that obtained in the reaction with halibut liver oil, and the two spectra were found to be identical.

Wald was also able to obtain cure of experimentally produced xerophthalmia in rats by feeding them small quantities of retinal substance daily for a period of fourteen days.

An interesting finding was that the proportion of vitamin A obtained from the dried retinal and pigment layers of the eye was thirty five times that present in the liver, an extremely high concentration at a site which is most sensitive to the presence of an early deficiency. It is evidence indicating the obvious importance of vitamin A for the integrity of the visual purple essential for protection against night blindness. No trace of carotene was ever demonstrated in the retinæ and pigment layers of any mammalian eye, with the possible exception of hepaxanthin. It is interesting therefore to note that some hepaxanthin always accompanies the vitamin A of fish liver oils.

(To be continued in June issue)

Clinical and Radiological Observations Concerning The Large Pendulum Movement of The Colon

By

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THE large pendulum movement of the colon—the only *unproductive* movement of that organ,—produces a longitudinal, pendular swing of the affected bowel segment, without transporting its content. In contrast to this, the other well known movements of the colon serve some *useful* purpose, either in the resorption or in the motor dynamics of the organ, by passing the content toward the rectum. The only exception, the antiperistalsis, creates—as its name indicates—a temporary retardation, in fact, a set-back in the transport, but manifests its usefulness in some other way.

The pendular swing affects as a rule only certain mobile segment of the gut, most frequently that of the transverse colon. The affected bowel swings out in a huge irregular arch, the two ends,—both flexures—serving as fixed points. The type of movement is designated as creeping, vermiform, snake-like or serpiginous in character. This huge change in the location or position of the segment results in no actual propulsion. The singular change demonstrated refers to a segmental locomotion, haustration, width, lumen, tonus of the gut remaining largely unaffected.

As a result of the pendular wave, the segment under consideration may evidence sweeping changes; a drooping, or a maximally descended or ptotic transverse colon, at successive examinations may change its location to such an extent, that the lowest point may move up from the levels of the symphysis to the height of the xyphoid process. The lowest point becomes the uppermost. In fact, the excessive swing may assume such proportions, as to render the gut-segment,—when viewed in this unusual location,—suggestive even to a pathological fixation. The absurdity of such allegations however becomes only too soon apparent, as a subsequent exposure may detect an entirely different configuration, inconsistent with any fixation. Similar findings may justify the correctness of Holzknicht's statement: "Nearly every pathological location or fixation of the colon has its double in the realm of physiology. Consequently assumption of any pathological position-anomaly is uncertain" (A. Koehler).

It is self-evident that during all these comparative examinations the technical details *must remain unchanged*. That holds true first of all for the *posture* of the patient, because postural changes alone "eo ipso" effect large variations in the position of the colon, especially in that of the transverse colon also under normal conditions,—without large pendular movement,—the transverse colon being lifted to a considerable degree, in the prone position, in contrast to that of the vertical position.

During the course of the comparative study the quality and the quantity of the opaque meal, its vehicle, the way of its administration,—whether oral or rectal,—whatever the case for the individual occasion may be, must not be changed. The phase of respiration is a further factor.

In both positions, whether prone or vertical, the usual postero-anterior views were used. A. Oppenheimer recently advocated also the lateral exposure for the study of the position of the colon. This view enables the visualization of the organ, in a *space*, instead of in a *plane*. It is self-evident, that the employment of this additional lateral view would increase both, the incidence and the degree of the cases of the large pendulum movement.

Analysis of the various movements of the colon.

Prerequisite for all the motor activities is the *muscular tonus* in the wall of the colon (Groedel, Pal).

Haustration—the expression of hypertonia—is not an active movement, it is much more the result of it. It does not further the transport of chyme, it rather retards it, but it promotes absorption.

The *small pendular movement* (Gottwald Schwarz), a fine, invisible, oscillatory, mixing movement transports the chyme in slow, hardly perceptible, nearly continuous stream, resulting in changes of the haustral markings and in formation of new, additional haustration (Braam Hooekgeest, Nothnagel, Canuon, Schwarz, v. Bergman and Katsch). These movements further primarily the digestion; evacuation being affected only to a lesser extent. In fact, according to Schwarz, this movement has no definite direction, it is a continuous churning, to and fro, a rocking, back and forth (Wiegephänomenon).

Haustrenflow (Katsch and Borchers's *Haustrenfließen*) may have *isomorph* and *polymorph* arrangement. The isomorph arrangement of the small haustral movement affects transport; the polymorph arrangement, identified as the mixing, or a to and fro churning movement, produces no propulsion. (Emmo Schlesinger attributes chyme flow also to the polymorph haustrenflow.)

Peristalsis of the colon, is in contrast to the peristaltic movements of the stomach and small intestines, not a well defined, independent movement. This term is often used collectively (for all the colonic movements), sometimes in general terms, occasionally even injudiciously. Peristalsis, a strong generalized contraction of the proximal colon, which, at the moment that food passes the valve of Bauhin, commences in a regular rhythmic fashion, is the forerunner, in fact, the basic substance, or the "conditio sine qua non" to the anti-

peristalsis, considered the chief colonic movement, in the cat (Cannon).

The "*promoting peristalsis*" (Bayliss and Starling), with exceedingly slow progress, is supposed to form an independent type of the colonic movements (Miklas).

"*Propulsive, slow movements*" (Fischl and Porges, Case), a subgroup of the peristaltic movements of the colon, further small thumb-sized fragments in the aboral half of the colon, where the content thickens into a plastic mass.

antiperistalsis is the main function of the oral half of the colon, in the cats, according to Cannon. This movement together with the haustral small pendular movement, effects a more thorough mixing, kneading, massaging of the contents, for the ultimate purpose, of having created a longer exposure time and a more thorough and intimate contact between chyme and resorbing surface of the mucous membranes.

"*The folds of the mucous membranes*" represent according to Forssell a momentary state of movements,



Figure 1—Case No. 1 (S.D.) Large Pendulum Movement of the Transverse Colon. A, 6 hrs. film; B, 24 hrs. film. Both taken in upright position. The highest point of the colon transversum on film A, becomes the lowest point on film B. Note the gas filling of the upper portion of the haustrated transverse colon, on film A.

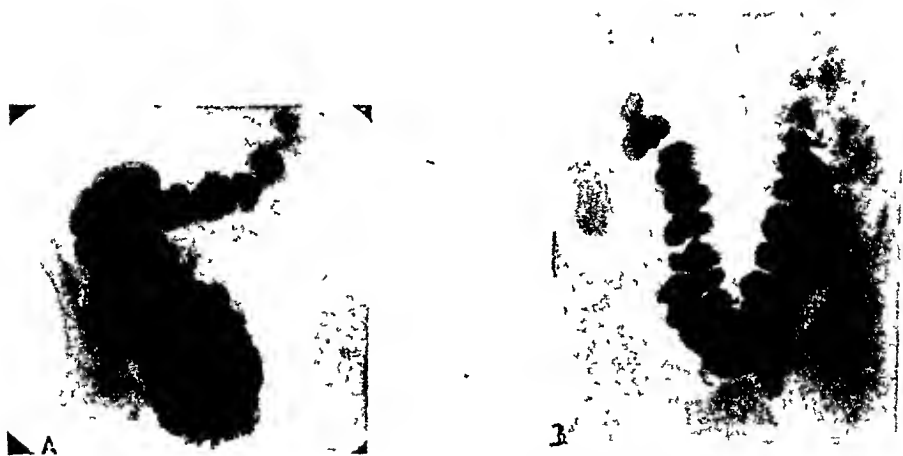


Figure 11—Case No. 2 (M.B.) Large Pendulum Movement of the Transverse Colon: A, 24 hrs. film; B, 72 hrs. film. Both, in upright position.

Holzkuoch's "*en masse*" movement, or the massive large movement of the colon, as well as the movement of the "*defecational act*" of Magnus produce large, extensive, powerful, rapid, massive, propulsive movements, both in exclusive service of the evacuation, as against the above mentioned movements, which serve both, evacuation and resorption.

The *antiperistalsis*, as noted over the proximal half of the colon, represents much more an active retrograde transport, (C. Jacobi, Cannon, Stierlin, v. Bergmann, Case) than a passive backflow (Schwarz). The

a factor, righteously considered influencing kinetic functions of the colon. The play of the folds may have a hitherto unsuspected significance in the control and propulsive movement of the gut. "The movements of the mucous membranes produce an extremely differentiated distribution and restraining of the food in the digestive chambers, of varying form and size and procure the fine regulation of the current by the passage of the contents in the alimentary canal" (Forssell).

The combination of all these motor functions together creates a teamwork, with promoting effect on

resorption, chyme inspissation and skybala formation, combined with a motor mechanism, which embraces a continuous chain from the invisible churning to the large mass movement. . . . the combined effort resulting in an enhancement for both, the absorption and the self-evacuation, considered the main functions of the large intestines. The oral half of the colon, distinguished by its abundant lymphatics, is, primarily adapted for resorption, the aboral half serves evacuation (Roith, Miklas). The importance of this com-

it is a rare observation, lending itself very rarely, if ever, to a roentgen snapshot, . . . the large pendulum movement of Rieder on the other hand represents a phenomenon, possibly, but not necessarily physiological in nature and although the incidence of its marked form is rather rare, however, if it does occur, it develops slowly and the fully developed picture of the large pendular movement remains stationary for a length of time, therefore its x-ray demonstration is easy.

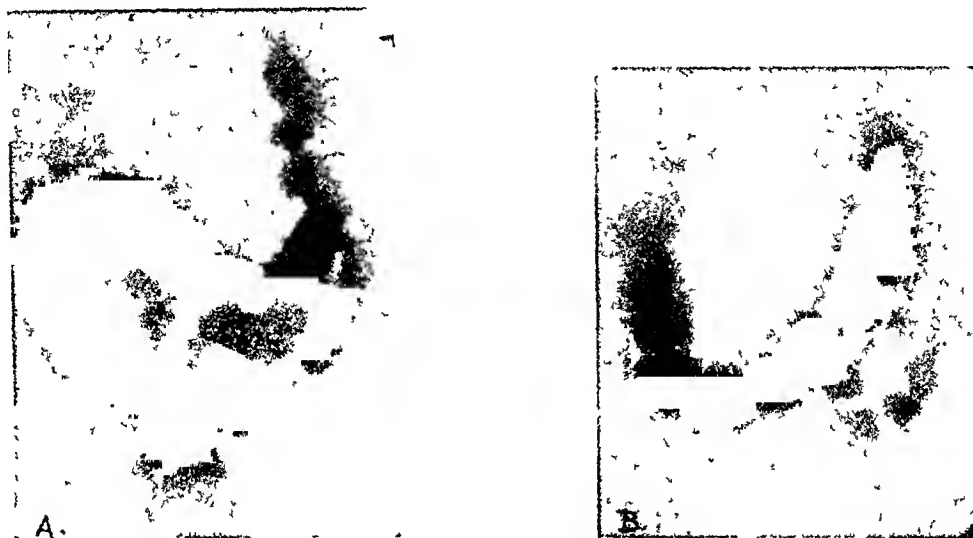


Figure III—Case No. 3 (B.S.) Large Pendulum Movement of the Transverse Colon, with redundancy of the hepatic flexure and descending colon, resp.; both films taken in upright position. A., 6 hrs. film. B., 24 hrs. film. Note redundancy as alternately demonstrated, the redundancy of the hepatic flexure on film A., and that of the descending colon on film B. Transverse colon droops on film A., toward the left side, on film B., toward the right side.

bined co-operation is best demonstrated by its failure, e. g. on administration of cathartics. Cathartics, as a rule, accelerate peristalsis, but halt antiperistalsis, whereby inspissation of the chyme suffers, the enhanced colonic transport results in frequent loose bowel movements.

The large pendular movement of Rieder represents, in certain respect, an opposite phenomenon to the mass movement of Holzknacht. The movement "en masse" produces—with or without a certain subjective sensation—a sudden, in fact, a lightning-like transport of the content, over an extensive area of the colon, at a simultaneous disappearance of the haustration and narrowing of the colonic lumen, while the location and the position of that segment, during this act remains largely unchanged,—a thrilling phenomenon, an unforgettable spectacle to observe it,—in the large pendular movement of the colon, haustration, lumen, width, size and external markings remain practically unchanged, the only changeable factor remaining the position of the colon segment, which is the end-result of an imperceptible, slow and invisible movement of the gut.

While Holzknacht's "en masse" movement is a physiological act, occurring daily, once or several times, always of a few seconds' duration only, consequently

Incidence

Rieder reported about his observation in 1912. He made serial examinations on two healthy individuals, the successive films being taken at about half hour intervals, with the observations extended over a period of 33 hours. He appended sketches to the first and original x-ray films to the second case. The pendular changes found, could be designated as marked, though not excessive.

Emmo Schlesinger in his excellent textbook refers to two observations of his own. In the second case, however, there was an obstructive process of the transverse colon present. The pictures with "stiffening" and "secondary exhaustion" are pathophysiological manifestations of an obstructive process of the lumen and may not represent a genuine large pendular movement of the colon.

A. Oppenheimer, who does not use the term of large pendulum movement, nor make any reference to Rieder's name, describes in his recent article quite a similar phenomenon observed over the colon, respectively over the individual segments of this gut and attributes these changes in the position of the colon as daily recurring, physiological changes, due to the filling and emptying of the segment in question and calls the receptive relaxation of the individual colon

segment, diastole, in contrast to the systole, which refers to the lightning-like mass-movement of Holzknecht. Latter movement, the systole lasts only for few seconds, while the diastole lasts 4 or 10 hours or longer.

Textbooks, German and English alike, do not dwell extensively enough on this subject. For some reason or other, this chapter has certainly been inadequately dealt with, as large textbooks at best, make only a cursory note, or short reference to this topic, or omit it altogether.

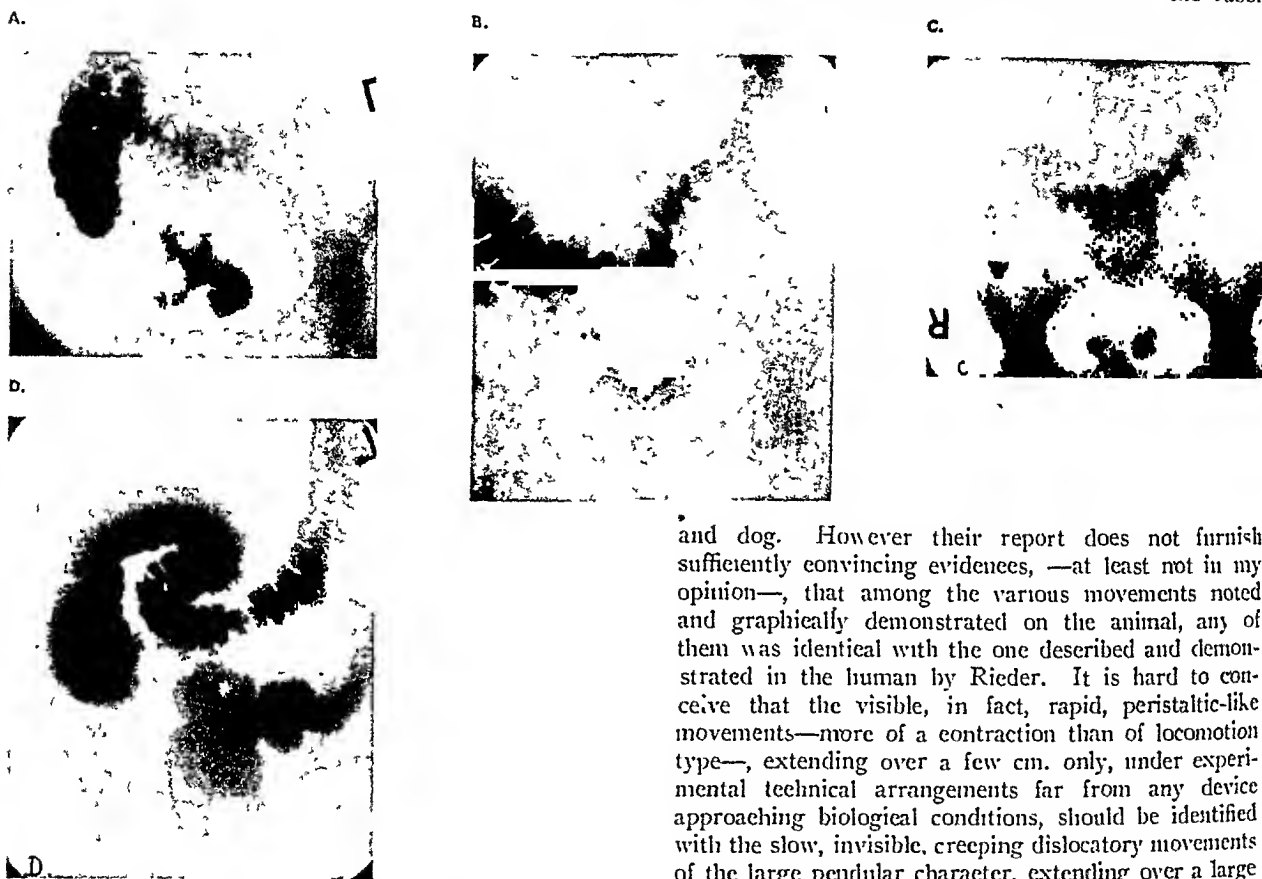


Figure IV—Case No. 4 (R.K.) Large Pendulum Movement of the Transverse Colon. A, B., C. films taken in upright; D. in prone pos. A., 6 hrs. film. B., 24 hrs. film. C., 54 hrs film. D., after barium enema.

This leaves the question of the *actual incidence* of this phenomenon entirely open.

As far as my own experience is concerned, upon following up this question during the last 12 years in a group of approximately one thousand cases of gastrointestinal import, . . . I would be loath to arbitrarily fix any definite figure as indicative of the frequency of this incidental finding. Transitions are common and hardly definable. The difference between the mild case and the one considered normal, is hardly discernible.

Mild degrees, definitely beyond the boundaries of the physiological variations were found to number approximately 10 to 15% of the total, while very pronounced cases with puzzling morphological manifestations were after careful search discovered in less than 2% of the total (18 cases).

Comments

The credit goes to Rieder for having the large pendulum movement in the human observed, defined and demonstrated in a masterly way, through his x-ray studies. It is claimed in certain quarters that similar movements were observed in animals during experimentation (Bayliss and Starling) or during observations through the transparent abdominal window (Katsch and Borchers). The former experimentators are credited for having been the first to observe the large pendular movement of the colon on the rabbit

and dog. However their report does not furnish sufficiently convincing evidences, —at least not in my opinion—, that among the various movements noted and graphically demonstrated on the animal, any of them was identical with the one described and demonstrated in the human by Rieder. It is hard to conceive that the visible, in fact, rapid, peristaltic-like movements—more of a contraction than of locomotion type—, extending over a few cm. only, under experimental technical arrangements far from any device approaching biological conditions, should be identified with the slow, invisible, creeping dislocatory movements of the large pendular character, extending over a large area. Consequently, I would say, that Rieder's observations have no counter part,—animal or human—, in the previous medical records.

A combined contraction of both, the longitudinal and circular musculature of the colon, with a predominance of the former, resulting in a noticeable locomotion, expresses the substance of this kinetic mechanism, which appears, as a rule, closer to the end of the digestion and affects a large, but circumscribed segment, usually that of the transverse colon.

One of the preconditions to the development of this phenomenon seems to be the presence of an *elongated mesentery*. In producing and explaining the large pendulum movement, the potential role played by the *mesenteric smooth muscle tissue* may prove of great importance too. Emmo Schlesinger emphasizes the *constant* presence of the smooth muscle in the mesentery of the *transversum*, in contrast to the other segments of the mesocolon, where this is of an occasional occurrence only.

Probably outside of the long mesentery and its muscle supply also the *abdominal space* may have its role in the position and in the free movability of the colon, especially as related to the transverse and ascending colon. According to Oppenheimer these segments, being in contact with the anterior abdominal wall, are strongly curved and turn forward in the stocky person with deep abdominal cavity in contrast to the slender

The regulatory mechanism of the colonic movements is undoubtedly under the influence of the *nervous system*. Even the animal experimentation upon isolated colons (Bayliss and Starling) can not be construed as conclusively contradictory to this assumption. Thomas and Kuntz found the intestinal contractility as an *inherent* property of the gastrointestinal *musculature*, after paralyzing the enteric nervous mechanism with

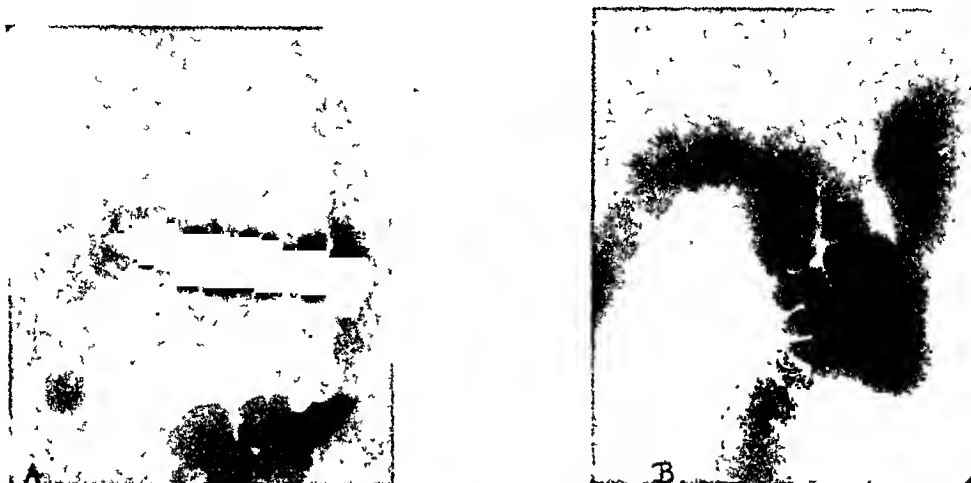


Figure V—Case No. 5 (M.G.) Large Pendulum Movement of the Splenic Flexure and Transverse Colon, associated with huge redundancy. A. film taken 30 hrs. after oral administration of the barium; B. flexura lienalis and the aboral transverse colon, after barium enema. (Note the tremendous redundancy of the flexura and the positional changes of the transverse).



Figure VI—Case No. 6 (S.M.) Large Pendulum Movement of the Splenic Flexure and Transverse Colon, associated with redundancy of the flexure. A. 24 hrs. film; B. splenic flexure exposed, after barium enema; C. splenic flexure, after partial evacuation of the barium; note the gas filled redundant coils of the flexure. Aboral half of the transverse in B. shows horizontal, on C. vertical trend.

subject's flat, long abdominal cavity, in which the elongation of the transversum results in descent of the gut. Accordingly constitutional factors may have their role also in the production, or at least in the roentgen demonstration of the large pendular movement. Of course Oppenheimer's lateral view films might detect huge dislocational movements of the gut segment, where heretofore—using the routine postero-anterior technic—their presence could even not be suspected. This necessarily refers to the spacious abdomen of the stocky person.

nicotine. The role of the nervous mechanism is clearly summed up (Editorial J.A.M.A. 1926, June 12) in a sentence: "The enteric nervous mechanism brings about variations in the tonus of the musculature and the amplitude and force of the contractions and initiates and coordinates peristalsis and other reflex movements in response to local stimuli".

Additional stimulating effects on the motor dynamics may be achieved under the influence of various, hitherto unknown or unsuspected factors, which may originate either in some intraenteral process,

such as a peripheral reflex stimulation through the mucosa of the colon (v. Bergmann), or in some other, extraenteral factors, as represented by various endocrine, metabolic, toxic, constitutional or psychic agencies. The inhibitory role of psychic factors, emotion, etc. on the colonic movements was experimentally proven in the cat by Cannon.

* * * * *

In Rieder's large pendulum movement the locomotor changes are conspicuous. Tonus, haustration are un-

with shortened taenia and is deeply haustrated, resembling the pilocarpin colon of v. Bergmann. The various classes entail certain predisposition into well defined groups of diseases, also a certain typical reactivity to the pharmaca of the vegetative nervous system (atropin, pilocarpin, physostigmin, adrenalin, etc.)

In Oppenheimer's grouping the position-changes of the colon or of its segments are quantitative, not opposite in direction, they are phasic in nature, subject to the physiological digestive phases. They harbor a

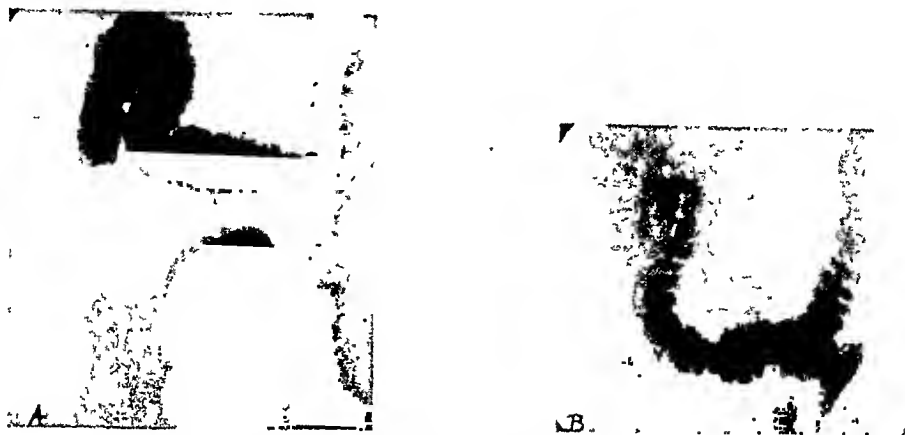


Figure VII—Case No. 7 (M.K.) Large Pendulum Movement of the Ascendent and Transverse Colon. Both films taken in prone position. A.: ascendent colon is high, hypodescended, not inverted and the transverse is high. B.: ascendent colon is high, inverted and the transverse is very deep.

affected. The drooping loops may show the same tonic, spastic, haustrated appearance, as,—at some other time—, the shorter, high transverse colon would,—with the same individual. Again, in some other cases of the large pendular movement with individuals of the atonic habitus an atonic, redundant colon may be encountered, which may elicit symptoms of stretching, decompensation, relaxation, sacculation, etc. (F. H. Kruse). The marked excursions, as noted in the typical cases, may point to an *opposite* direction. No time element is noted. Regularity or cyclicity of the appearance is missing.

Pharmaca, such as atropin, pilocarpin, etc. affect the position of the colon or of its segments, too; however this is coupled with *tonus changes*. With the increased tonus (e. g. from pilocarpin) the haustration increases, the gut-segment shortens and the position of the gut becomes elevated and straighter, and vice versa.

The *constitutional* factor, as expressed by various types of habitus (Stiller), or of tonus (Schlesinger's roentgen-stigmata), or of the imbalance of the vegetative system (Eppinger & Hess' vagotonia), or of the general visceral ptosis (Glenard's splanchnoptosis), etc. may and does have its earmark on the position and appearance of the colon, alike. A ptotic colon is generally considered the stigma of a habitus asthenicus or that of a splanchnoptosis. However, the drooped colon of the sympathicotonic condition exhibits at the same time signs of relaxation, unhanstration, like the atropin colon of v. Bergmann. The transverse colon of the hypertonic's of Schlesinger is high, straight, lifted.

seemingly contradictory element, namely: that the passively receptive segments during the so-called diastolic phase show haustration, signs of a hyperactive state, although on the sagging loops unhanstration, passive dilation, sacculation would be the logical sequel. During the passive, receptive diastolic phase the colon segment droops elongates, like the atropin colon would; its increased haustration, however, behaves like a pilocarpin colon does.

* * * * *

Six or eight hour films show the transverse colon, as a rule, at a higher level, than the later, the 24-48-72 hour films do. At its higher level the transverse colon may be found straight, curved, ovoid, spherical or irregular, the later exposures, in positive cases showing various degrees of sagging tendencies, may reveal an angulation, with a sharp angle pointing downward; at times, multiple angulation is noted; gyration, S. or W. shape are the other types of the configuration. In few cases the opposite trend is found, and the *later* films may elicit signs of a more sthenic character.

The detection of the large pendular movement is always incidental. There is nothing in the history or among the symptoms or signs which is typical and there are no co-existing diseases or signs, which might be called suggestive, or being in causal correlation, as a causative agent or as a product.

I have found among my cases of marked large pendular movement co-existing cancer of the stomach, peptic ulcer, dysentery, chronic appendicitis, constipation, chronic hepatopancreatitis with diabetes mellitus, in-

packed ureter stone, redundancy, megasigmoid, nemas-thenia, developmental malformations, such as undescended or inverted cecum. In other cases only vague symptoms were present, not indicative of any well defined disease. Occasionally no gastrointestinal symptoms were complained of.

Significance of the large pendulum movement

The knowledge of the large pendular movement

2) Cancer or other tumor, ulcer, diverticuli or any other pathology, seated over the mobile segment, may give during a *repeated examination* within a few hours an *entirely different location of the positive palpatory findings*. Without this knowledge no explanation or diagnosis could be offered for cases in which a tumor palpated above the umbilicus, at some other time at or above the level of the symphysis would

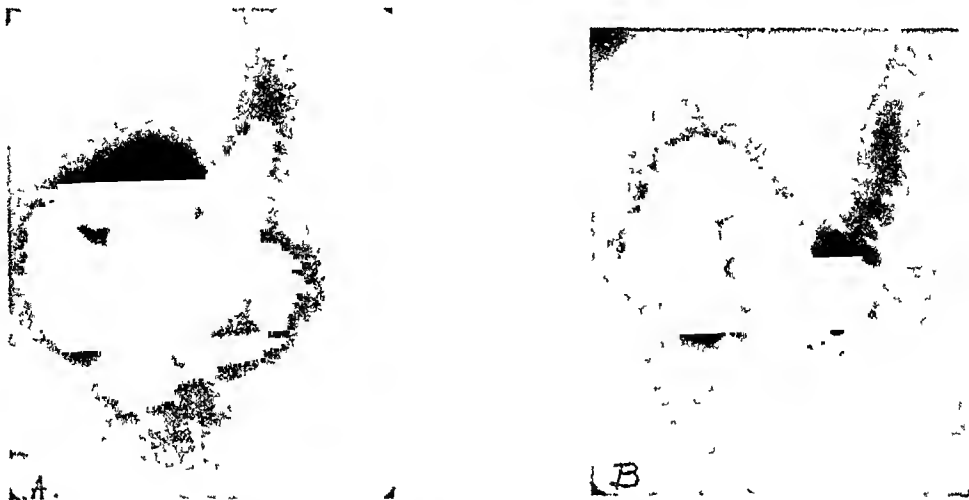


Figure VIII—Case No. 8 (S.L.) Large Pendulum Movement of the Colon, associated with redundancy of the transverse and descending positions. Changes are of moderate degree. Both films taken in prone position. A., after barium enema; B., after defecation, subsequently.

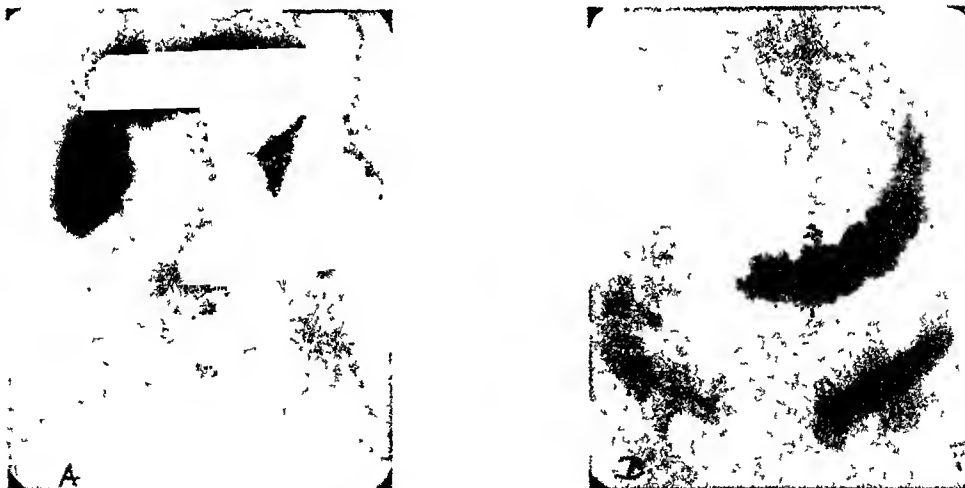


Figure IX—Case No. 9 (E.P.) Large Pendulum of the Colon Descendens, associated with huge redundancy. Both films taken in prone position. A., after barium enema; note the configuration of the convoluted coils of the redundant descending colon; B., postdefecational film; note Holzknecht's "en masse" movement at three different locations of the colon. Redundancy disappeared without a trace.

seems to be important both from the scientific and the practical-clinical point of view.

The points of importance may be summed up, as:

1) The fact itself, that an anomaly or peculiarity, producing far reaching positional and morphological changes of an organ in its appearance, or in its x-ray demonstration,—the only way of its recognition—, may exist in the system, which may mislead one in the interpretation of the puzzling findings.

be located, even possibly crossing the middle line. In another case a palpable tumor of a flexure region may at some other time be missed, when same may move behind the rigid thoracic wall, in the hypochondrium. Beware diagnosing a patient as merely hysterical because of such puzzling or confusing symptoms or signs.

3) A long mesentery, the prerequisite for the large pendular movement, is equally indispensable and is invariably present in *redundancy of the colon*. The

colon, with an elongated mesentery may at any unchanged position show variation in shape only, (festoon, gyrated, curled upon, etc.) as encountered in redundancies, . . . or at an unchanged haustration and lumen in position only (high or low or laterally displaced, etc.), as one finds in large pendulum movements, . . . or in combination of both.

While not every large pendulum movement implies a simultaneous redundancy, *practically all redundancies are potential sources of large pendular movements.*

4) . . . Redundancy may predispose to the development of *volvulus* and to a lesser extent to *invagination*. This seems to be a fairly established fact. No intussusception or extensive torsion can develop unless an elongated mesocolon furnishes a basis for this intestinal dislocation, usually in presence of developmental malformations (Pratt and Fallis). The elongated mesocolon, a precondition to redundancy and volvulus, is similarly a precondition to the large pendular movement of the colon. Is it after all not reasonable to assume that a possible causal correlation

may equally exist between the large pendulum movement and a potential *volvulus* of the colon?

Conclusions

The large pendulum movement of the colon described by Rieder in 1912 remains a rather neglected field in the literature.

Its incidence, clinical importance, differentiation and its place among the other types of colonic movements has been stressed and its roentgen-demonstration illustrated on a series of films.

It is not a regular physiological movement; still its occurrence does not necessarily imply pathology.

Its milder form is common: in fact, within certain limits it may be considered physiological; the extreme degree is rather rare. It may mislead one in the interpretation of its x-ray demonstration,—the only way of its recognition—, and in the clinical diagnosis of any disease, located within this mobile, pendular segment of the guts.

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Reflections on Geriatrics in Internal Medicine

By

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I WAS at first rather hesitant about presenting little more than an idea, but I believe the subject at hand is worthy of repeated consideration. I am urging an increase in specialized study and practice of the medicine of the aged-geriatrics. It is unnecessary to reiterate the limited reference of the concept of time. The life of the dog lasts some fifteen years, of man, three score years and ten, more or less, and eternity is as a minute in the life of the Almighty. Dr. Bernard Sachs, after sixty years of service, declares, "The joy of work is the joy of life. Don't let the biblical three-score and ten affect you. To add to the years, stop counting them." Old age is a condition, a biological situation, and calls for as fresh and as special an approach as does infancy. When we realize that a disease can be understood only in terms of its host, it becomes apparent that the common cold, gastric disturbances, cardiac aberrations have different meanings and implications in the young, the youthful, the middle-aged and the old. Thus it is that the student and healer of diseases of the aged faces a fundamentally different situation: we have recognized this fact at the other end of the life scale. We have specialists in pediatrics, pediatric clinics, pediatric societies, pediatric journals, institutions of research, professorships. I urge that the same be done for geriatrics. Only in this way, through specialized, undivided study, can we achieve progress in understanding, and perhaps meeting, the health problems of the aged. If we are to move, even slowly, toward the realization of the dream and hope of extending further the active life period, we must undertake special study of the problems of the latter part of that period.

The terms geriatrics and gerontology are often erroneously used interchangeably. While the former concerns itself with diseases of the aged, the latter treats of the scientific approach to an understanding of the genesis of old age. As Dr. Steiglitz tersely defined it, "Gerontology is the science of aging." Senescence, "the process or condition of growing old," is therefore the subject matter of gerontology. It was Nascher of New York who in 1914 gave the name geriatrics to the study of diseases of the senile organism. The stimulus to this work was the notion that when an old person complained he was considered to be suffering from "old age" with no measure available to alleviate his suffering. Nascher speaks of senility as a physiological entity like childhood. Paradoxically, it's a case where degeneration is normal. Therefore, we do not face pathology complicated by degenerative phenomena, but pathological processes superimposed on a normally degenerating body economy. This concept of geriatrics stands regardless of the duration of the pathological process. Geriatrics may thus be de-

fined as a division of medicine dealing with the diagnosis and treatment of disorders peculiar to old age, and of other disorders in the light of the peculiarities of old age.

The period of manifestation of senescent changes is rather indefinite, and the concept of senility as a physiological entity rather than a pathological state of maturity has been complicated by our inability to define the senile norm, and by our inability to state when senility begins. But it is obviously necessary to apply a notion of physiological rather than ordinary chronological time. Senility must therefore be precised for each individual case, until such time as norms are defined and accepted. The aged are not exempt from the infections found in early life, and progeria—a rare condition in which a person may be old in early childhood and die, aged, while young in years—is a striking example of one's being at once old and young, in the two senses of time. We may hazard a definition of normal senility as being that state wherein organic or functional decline cannot be traced to anatomical or pathological physiology.

Thewlis reflects on neglect of the aged, noting that most physicians treat them as they do the young, and when the patient dies, attribute it to "old age" not realizing that the organism demanded quite different drugs and handling. He rightly maintains that old age is neither a disease nor an effective cause of death. Martin divides the tragicomedy of life into three acts: first, evolution; second, maturity; third, involution. We administer adequate attention to the first act, reasonably fair mindfulness to the second, and become indifferent to the third. To indifference we may ascribe the fact that the subject of disease of the aged is blended with general medical practice. In the same vein an editor reflects, "Geriatrics has been a neglected field of medicine. At present the mortality at advanced age is considerably more than necessary, owing to neglect to special study in the anatomy and physiology of senescence . . . Old age has been shelved as useless in a society based on material standards." It is as a result of control of infectious diseases in childhood, guided by the public health offices and pediatrics, that mortality in early life has been conspicuously reduced. The young mother need no longer fear the "summer complaint" her own mother has not forgotten. A glance at the history of infectious diseases illustrates the effectiveness of research and the institution of preventive rather than curative pediatrics. We have not, however, instituted preventive geriatrics, for the period from forty to sixty. It is in these years, or even before, writes Stieglitz, "that the involutional processes start, later to reveal themselves in the more obvious evidence of aging." Admittedly, preventive geriatrics does not mean the prevention of aging, but retardation

of premature senescence, and control of the process of aging. Old age is, I believe, moldable into a form made graceful, and acceptable to the old. "The act of growing old graciously is not an extemporaneous event but one that merits deliberation," writes Willus. He has graphically presented the phases of activity and declivity of life in an arbitrary biologic curve which if closely followed means the adoption of a "protective philosophy of life." The individual who premeditatedly follows the biologic curve and makes the necessary restrictive adjustments in life, has adopted a more advantageous mode of living than the one who willingly or unwittingly ignores the mandates of nature and plots his chosen curve of activity. Walt Whitman wrote,

"Youth full of grace, force, fascination!

Do you know that old age may come after you with equal

Grace, force, fascination!"

He disagrees with the current concept that senescence implies declivity. One may point to compensatory activation of certain physiological phenomena. One may mention the brilliant achievement of such men as Michelangelo in the arts, Jacobi and Keen in medicine. Oliver Wendell Holmes in statecraft, at very advanced age. In ancient Greece an old man was a rarity. Owing to increased life expectancy, the aged are very much with us today. In fact, they harbor a fear that they may live too long, hence the clamor for economic security, and the complaint against economic processes which have their own peculiar concept of time. When man becomes aware of palpable physical deterioration, he begins to suffer psychologically. The knowledge of physical regression is a source of poignancy to persons in maturity. Thorough study of gerontology, on which preventive geriatrics is dependent, would help to bring the physiologic age up to par with the mental alertness of the individual. Because the many chairs of pediatrics in the medical colleges find no counterpart in the study of diseases of old age, we fail to separate physiological from pathological old age, not so much for lack of knowledge as because of poor utilization of that we possess.

A survey by the writer six years ago disclosed that in the last two decades there had appeared, in the United States, Great Britain, France, Germany, Italy and Russia, seventy-seven textbooks on pediatrics, ten on geriatrics. In the indexes of the Surgeon General's Library at Washington we find no journal specializing in geriatrics, fifty-five in diseases of childhood¹². Our lack of interest has led us all too frequently to raise the question of mental decline, and age itself, as an excuse for our ignorance.

In dealing with symptomatology in the aged we must be aware of systemic interrelations, we must learn to respect vagueness in the description of symptoms. Vague phenomena often seem to lack clinical meaning, and are seldom recognized for what they are. When we finally come to treat these patients the evidence is often palpable, the condition frequently irremediable. But if geriatrics is studied, and physicians become aware of its importance, the opening scenes

will not escape detection, their implications will be understood while the condition is still in a reversible stage. While some stages are not curable, they can be controlled. The ability to be a good listener is of the utmost importance in taking a history, particularly when listening to an elderly individual. Let the geriatric patient relate a long and possibly confused story of ailments. He has probably all too often had his troubles passed over as senile complaints. The patient must be understood, his functional disturbances and physical defects detected and properly interpreted. Lambert gave excellent expression to this basic concept of clinical approach in stating: "... the pharmacology of the aged demands more of the art of the practice of medicine than in any other group of patients. One must learn to unravel the real from the imaginary, and one must learn to listen to many reiterations, but the mere fact of willing attention, cheerfully bestowed, is often in itself the best remedy to rule out many ills." With this type of clinical attitude we might discern the precursors of premature decline, and there are three particular conditions in the old, which often escape timely diagnosis, to which I should like to allude: thyroid dysfunction, achylia gastrica and hypertension. C. H. Mayo, in an address on the thyroid, said that "All fires, whether those of our own bodies or otherwise, must have oxygen for combustion. If you are talking to people from forty to sixty years old, and you ask them something quickly, and they look at you with their mouths open and ask 'What?', and they ask it a second time . . . give them a metabolic test . . . It is most interesting to see these people who have burned out their thyroids, without any pain or recognized trouble, but the chemical action is gone."

Achylia gastrica and essential hypertension and vascular disease merit particular mention, because they so commonly occur without symptoms. Were they kept in mind by the clinician examining patients in the fourth and fifth decades of life, and treatment instituted, a break in the compensatory mechanism which accounts for the absence of symptoms, might be avoided. When a person over forty complains that food is tasteless and insipid, unless highly seasoned, it may be viewed as suggestive evidence of a degenerative process of the glossal components of taste. Such a phenomenon may be regarded as portending gastric atrophy. Ascertaining the gastric chemistry even on the basis of such evidence, might well establish an achlorhydria, a valuable finding from the viewpoint of preventive medicine. The writer reviewed 17 case records indexed "Involutional Achlorhydria". In some of these intubation was for various reasons contraindicated. Others stubbornly objected to the procedure. The entire group presented a clinical pattern of hyperacidity, but nonetheless hydrochloric acid was prescribed with meals, before, during and after, with resultant alleviation of the dominant gastric complaints. It is apparent that, on clinical criteria alone, without laboratory support, the diagnosis stated was warranted. Ivy states that Gastric acidity declines after age 20, that achlorhydria increases considerably after

age 40, that by 65 over one third have no acid and over one-quarter do not respond to histamine.

Because of the insidious and asymptomatic onset of essential vascular hypertension efficient therapy may be deferred for years. No symptoms may arise until circulatory embarrassment arrests attention. Pathological physiology precedes cellular disease, a functional disturbance is unidentified. When well defined symptoms appear on the horizon, when sclerotic changes affect the vasa vasorum of the coronary arteries—since these concern themselves with nutrition of the heart, paradoxically, the heart which needs more nutrition, obtains less because of arteriosclerosis. Hypertension is no longer potential, but kinetic and actual. There is a prevailing opinion that arteriosclerosis is an expression of aging of the arteries, and not merely a transformation attending the process of aging. But "it is not a mere infirmity of old age, but rather a disease of the vessels manifesting itself mainly during senescence."

These three conditions point to the wisdom of thinking in terms of physiological old age, even when a patient is less than forty chronologically. Acquired achylia gastrica and essential hypertension may be curable in the evolutionary phases, but be recalcitrant to therapy once anatomical changes have taken place. Since one may be chronologically young and physiologically old, or vice versa, we must carefully distinguish between these conceptions of age, and apply the principles of geriatrics to all who are physiologically old. No set age may be stated, and each case must be analyzed from the standpoint of physiological advancement. The phase of life to which geriatrics applies does not begin at any special time. Senility, like childhood, is a physiological entity and not a pathological state of maturity. Geriatrically, diseases are pathological conditions in a normally degenerating body. The objective sought in geriatrics is not the restoration of a diseased organ to the norm of maturity, but to the normal state of old age. In one respect, both geriatrics and pediatrics concern themselves with problems of tolerance. There is however, a distinguishing feature characterizing the extremes of life, pointed to by Brown and Dolkart. They write, ". . . in the aged, the low level tolerance to metabolic and physiologic disturbances is accompanied by a concomitantly low level of regenerative capacity." Both extremes cannot be treated alike although they may harbor the same disease. To obviate hypostatic pneumonia, it frequently is wise to shorten the aged patient's stay in bed. The writer concurs with the above mentioned authors that a patient who reaches the ripe biblical age with positive serologic findings "Should be treated cautiously if at all." Soma Weiss refers to a type of dyspnea occurring in the aged with coronary disease after prolonged rest, ". . . a manifestation of congestive heart failure induced by rest (paradoxical cardiac failure)." Heat equilibrium is so much more easily disturbed in the infant, and heat production may be much subdued in the aged, both having the same lung pathology. In the aged, a non-visualized appendix, roentgenologically, has a different

clinical meaning than non-visualization in the youth. In the aged, infection travels less rapidly because of the fibrous degeneration of the tissues. The spleen in the aged is usually so small that in the various disorders associated with splenomegaly it cannot be discerned. Clinical evidences of left cardiac failure are so mild in the aged that they mimic other maladies, notably upper respiratory infections. Recognition of this phenomenon is conducive to adequate therapy. It is important to recognize that skeletal demineralization produces diminished vigor with which to withstand the storms and strains of physical activity and accounts for a rising disability conditioned by pathologic fractures. The fact that the aberration is amenable to therapy is sidestepped only because, as pointedly stated in an editorial, ". . . We have been accustomed to accept skeletal demineralization as an inevitable accompaniment of advancing years and have made too little effort to understand or prevent . . . protracted mineral starvation." We dispose of it under the label of osteoporosis. It may be well to point out that hypocalcemia in the geriatric patient and its relationship to a gradual depression in the hydrochloric acid in gastric juice as age ascends may result in poor absorption of calcium and thus establish a factor in the genesis of osteoporosis. Examples of the physiological significance of aging are too numerous to cite, but these given are typical. Similar pathology may display different symptoms and signs in different periods of life. Brown and Dolkart² have thrown into sharp focus the indiscriminate administration of sedatives to the geriatric patient. The general therapist is too often unmindful of the fact that since the aged patient is a relatively settled individual and not ordinarily labile, nerve sedation is not called for. Such medication is apt to be harmful. The writer recalls two male patients, 71 and 73 years old. Dysphagia played the dominant role in the symptomatology in both cases. They were indulgently treated with nerve sedatives for several months, when finally a diagnosis of carcinoma of the terminal esophagus was made. One received a palliative operation to the patient's satisfaction for over a year, the other was administered an abundance of compassion by the physicians who were closely related to him, and who permitted him to starve to death. In both cases dysphagia was interpreted as a spastic phenomenon, local or remote in genesis. Sedation is harmful because increased permeability in the aged is one consequence of cerebral arteriosclerotic changes—a defect in the integrity of the vascular system—conductive to low tolerance for bromides which diffuse more rapidly from the blood stream to the cerebrospinal fluid. The same holds true with other therapeutic agents. Because of slow metabolism in the arteriosclerotic, harm to the patient arises from the prolonged cumulative effect of the drug. In this connection it is worth recalling the common experience wherein peptic ulcer in the aged often produces severe gastrorrhagia, owing to arteriosclerosis of the gastric blood vessels. The rigidity of the sclerotic vessel wall will favor continued bleeding and surgical interference may be the procedure of choice despite the advanced

age of the patient. One must remember that the pulse in the aged with gastric hemorrhage differs from the pulse rate in young. A fast pulse is usually absent in the aged, conveying the impression that the hemorrhage had ceased and lulling the examiner into a false sense of security.

Were modern medicine to operate adequately, it might well prove capable of making equally graceful the two extremes of life. One reason that pediatrics is well established as a specialty, aside from the economic and social demand for it, is that the name has been given to this phase of medicine, and formal study operates under this name. This is sorely needed in diseases of the aged. A name causes emphasis, its absence, oblivion. Our great progress, over the last century and a half, in extending the term of active life, has been almost entirely owing to achievements to medical and social improvements dealing with childhood and young adulthood. It has been too easy to assume that if we set a human vessel on a true course, it will automatically follow it to its greatest possible limits. We have built the child, guarded the adult, and assumed that the events of old age would be a simple consequence of previous life. Let us guard

and study the aged too, and I wonder how much we may accomplish! An interesting and immensely worthwhile field for study lies open before us. I hope we shall not neglect it. In a note on the same subject in 1938, the writer suggested the following conclusions. They are still valid.

1. A closer knowledge of the physiology and pathology of the old is as essential as that of infant and child, and must be closer yet, for the intricacies created by the complications and sequelae of diseases of a lifetime leave footprints in their wake, and render diagnosis more difficult and therapy speculative.

2. The subject of diseases of old age is entitled to special study that would destroy the common attitude that "old age is a regret" and, that is about all there is to be said.

3. The subject has not received adequate attention in medical literature.

4. Medical colleges have all sorts of chairs, but none for the old man.

5. Given specialization, geriatrics should receive due recognition, on a par with other branches of scientific medicine, and the subject should be included in college curricula.

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13. The writer received the following letter from Dr. Archibald Malloch, librarian of the New York Academy of Medicine. "Disregarding all text books written before 1900, and those containing less than 150 pages, we find that the card catalogue of the Academy Library contains approximately 98 books on pediatrics, as against 31 on geriatrics. In counting the periodicals we ignored the time of publication. We found approximately 200 periodicals in the field of pediatrics, as against 4 on geriatrics." Comparison of these figures with those from the Surgeon General's office indicates some progress with regard to books, but very little progress with regard to periodicals.

Changes In Liver Function Test During Sulfonamide Therapy

By

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(Digested from *Ann. Int. Med.*, 19, 4, 622-628)

ALTHOUGH there have not been many reports of liver damage occurring in patients under treatment with sulfonamide drugs, such damage does occasionally occur, and it was thought wise to use the functional liver test of Gray (1) to detect early signs of such hepatic changes early in the course of treatment, especially since the evidence offered in the previous paper points clearly to serious damage at times in those patients who are idiosyncratic to these drugs. Liver

damage causes an alteration in plasma globulin, and Gray's test is one in which colloidal gold is precipitated by the diluted serum of a patient with hepatic disease but not by normal serum.

RESULTS

One hundred and six patients were tested. Seventy-three of these children with negative initial readings were tested periodically during treatment with sulfa-

thiazole or sulfadiazine. Twenty-four of these children developed slight to markedly positive readings in from 3 to 23 days of treatment (see Table I).

TABLE I

Data on Patients Developing Positive Colloidal Gold Reaction of Serum During Therapy

(a)

No. of Patients	Clinical Diagnosis	Age	Sulfa-diazine in gr.	Sulfa-thiazole in gr.	Ther. appy in Days	Colloidal Gold Reaction	
						Initial	Final
7	Broncho-pneumonia	7 Mo. ¹	28		6	332	543
		8 Mo. ¹		40	3	322	532
		7 Mo. ¹	90		8	322	533
		5 Mo. ¹	97		3	322	454
		12 Mo. ¹	160		10	322	522
		6 Mo. ¹	165	168	23	222	554
		4 Yr.	390		6	322	532
1	Acute otitis media	2.5 Yr.	754		23	222	544
1	Diphtheria	11 Yr.	707		10	322	554
1	Tuberculous pneumonia	8 Mo.	243		17	332	533
1	Retropharyngeal abscess	7 Mo.		92	14	322	542

(b)

7	Broncho-pneumonia	3-30 Mo.	(5) 67-331		6-11	332-322	422-433
				(2) 111-225	4-7	322	
1	Lobar pneumonia	8 Yr.	450		7	322	432
1	Influenzal meningitis	1 Yr. ²	1121		15	322	422
1	Scarlet fever	10 Yr. ²	536		11	322	433
1	Pertussis	30 Mo.	277		11	222	422
1	Pharyngitis	4 Yr.	389		12	322	422
1	Otitis media	10 Mo.	68		3	332	433

¹ Reaction had returned to normal within three months.

² Necropsy.

Out of the 11 patients who gave the more positive reactions (Table I, part a), four returned to the hospital in 2 to 3 months and were retested. It is interesting that all four had negative reactions, thus showing the capacity of the liver to repair. The thirteen patients in Table I, part b, showed slight changes in the colloidal gold test, and this was probably indicative of early liver damage because the necropsy findings in one fatal case showed a beginning central necrosis on a background of hepatic cellular dissociation. There were no significant changes in the hemotological picture in any of these cases. Among the 49 cases which did not show positive colloidal gold tests, one died and the necropsy did not show much evidence of hepatic damage,—merely some granular degeneration of the cells and a moderate serious hepatitis.

In 13 per cent of the patients studied, positive tests for altered liver function were obtained. There was no correlation between the amount of drug used or the time over which it was given, to the liver damage, which must depend upon idiosyncrasy. Certain experimental work suggests that a high protein diet and one containing adequate vitamin B-complex may protect the liver to some extent from damage by certain of the sulfonamides. Obviously attention to diet as well as the use of liver function tests would be of value in treating children with these drugs.

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Notes on Nutrition

Dental caries is a major problem in public health, and caries has not lessened in its incidence during the past several decades. The exciting factors are bacteria, capable, by their metabolic products, of destroying tooth substance, and substances within the mouth which can be converted into substances harmful to the teeth. Predisposing factors are those which exert their influence through systematic or nutritional channels and certain local factors whose effects are exerted in the immediate environs of the tooth. (*J. Am. Dental Assn.*, 30, 25, 1943). In diabetic children observed over a 17 year period, dietary measures practically did away with caries by hardening the dentin. (*J. Am. Dental Assn.* 30, 670, 1943). The diet used was liberal amounts of milk, eggs, meat, vegetables, fruit, and cod liver oil daily. There was reason to attribute the improvement noted directly to the diets used. There was no evidence of any significant correlation between the level of fluorine supply and the extent of the caries. The restriction of carbohydrate probably really was not a factor, for in many of the experiments liberal carbohydrate was permitted. In a series of normal children, similar diets, not restricted in carbohy-

drate, seemed to produce equally good hardening of the dentin (*J. Am. Dietet. Assn.*, 18, 211, 1942). In some special experiments, the actual feeding of very high glucose intakes did not promote caries. (*J. Dental Research* 22, 45, 1943).

Electrocardiographic changes associated with thiamin deficiency. Slowing of the heart rate in some degree occurred in all thiamin-deficient pigs (*Bull., Johns Hopkins Hosp.*, 73, 169, 1943) (*Am. J. Path.*, 19, 341, 1943). This was more marked than in pigs fed low caloric diets but protected with adequate B vitamins, or than in pigs growing poorly because of deficiencies in pyridoxine, pantothenic acid, or riboflavin. Severe bradycardia, however, did occur in extreme inanition, although adequate B vitamins were provided. Prolonged P.R. intervals, as well as second degree AV block were common in thiamin deficient pigs. The following changes also were noted in thiamin deficient pigs, and they became less marked, as the deficiency was altered,—high voltage and broadening of P₂; widening of Q.R.S.; inversion of T; premature contractions of nodal and ventricular origin; AV dissociation; complete heart block; bigeminy; and even auricular

fibrillation. The injection of atropine sulphate, in cases of inanition and in cases of thiamin deficiency, was followed by increased heart rate and shortening of the P.R. interval. Obviously, thiamin is important for the heart of the pig. Bradycardia may be a means for sparing the heart under unfavorable conditions of thiamin deficiency.

"Dairy Merit", a new concept in milk production efficiency. A high ratio between milk-energy produced and food-energy eaten is "dairy merit". In the cow the food eaten is usually roughage that humans can't eat. For these reasons, especially since a good cow can produce in milk 33 percent of the energy eaten as food, milk becomes a desirable product, especially since its benefits are so well recognized. But changing stock food into edible meat is much less efficient, only 15 percent of the food-energy being obtained as meat energy. Hence, in a world food crisis, grains which can be eaten by humans should be fed to them directly, not converted into beef or pork. (Missouri Research Bull., No. 366, 1943).

Jaundice in pneumonia. Some experiments were done on dogs which suggest that jaundice in pneumococcus pneumonia is less, and hepatic damage is less in animals whose livers have been protected by adequate diet prior to the pneumonia, than in those who were maintained on inadequate diets previous to the disease. (South. Med. J. 36, 603, 1943). The series of experiments was inspired by observing a very high incidence of jaundice in pneumonia in negroes who had subsisted on inferior diets.

Errors in calculation of the nutritive value of diets. An interesting experiment was made to compare the estimated food values with the actual, analytical values, using 20 meals as a basis, and it was found that while agreement for calories and protein was fair to good, the value of fat was over-estimated in theoretical calculation, and carbohydrates were underestimated. In the case of ascorbic acid, the analytical values turned out to be only 24 percent of the theoretical as calculated from tables. In the case of iron, the theoretical approach was close to the actual analytical results, provided that 21 meals were analyzed. (Canad. J. Pub. Health, 32, 362, 1941; 33, 224, 1942; 34, 367, 1943).

Phytic Acid and Iron Absorption. Since iron phytate is currently used in the food enrichment program, it is of interest to note certain experiments in human feeding which suggest that feeding sodium phytate reduces the full absorption of both ferrous and ferric iron, especially marked in the latter. Phosphate had a similar, though less marked, effect. Lancet II, 126, 1943).

Riboflavine in ocular tissues. A determination of the riboflavine content of various eye tissues showed highest amounts in the cornea and in the Meibomian and

lacrimal glands. This suggests that the cornea obtains its riboflavine from the eye secretions, not from the blood supply (Biochem. J., 37, 250, 1943).

Counteracting the effect of dicoumarin. The untoward effects of too large a dose of dicoumarin may be counteracted by the injection of the natural vitamin K₁ oxide (New England J. Med., 229, 353, 1943); a transfusion of fresh blood also has the same effect. The synthetic vitamin K appears to work too slowly to quickly neutralize dicoumarin.

Protein and hemoglobin formation. An adequate amount of dietary protein seems to be essential for normal hemoglobin formation (J. Nutrition, 26, 21, 1943). In an anemia produced by deficient protein in the diet, iron has no therapeutic effect. Such an anemia cannot be produced by simple inanition. A certain amount of protein is needed for hemoglobin formation.

Perosis. Perosis, also known as "hock disease" or "slipped tendon" is a bone disease occurring in chicks, and may result from a deficiency of manganese, choline, biotin, or perhaps two or more unknown dietary factors. (Science, 84, 252, 1936) (J. Biol. Chem. 134, 459, 1940) (Proc. Soc. Exp. Biol. Med., 49, 231, 1942) (Univ. of Mo. Res. Bull., No. 343, 1942) (Poultry Sci., 23, 88, 1943).

Relations between feed, livestock and food. Dwindling supplies of livestock feeds seems to suggest a restriction in future livestock production for meat purposes, and the use by man of proteins directly from vegetable and cereal sources, in order to make available food supplies go further in the world food crisis. About two-thirds of the feed used by live-stock is not suitable for direct human consumption,—hay, pasture, mill feeds, and other feeds that are converted into meat, eggs and milk. Hogs and milk cows are the most efficient converters of feed into food, considered from an energy standpoint. But, considered from the standpoint of protein food produced, milk cows are the most efficient, followed by turkeys and chickens for meat and for eggs. About 12 to 15 pounds of grain must be fed to livestock to produce enough meat and other livestock products to support a man for one day, while 2 to 3 pounds of grain eaten directly will support a man for this period. The extent of the shift in American food habits may be determined by the extent to which we are committed to prevent starvation and to supplement other food supplies abroad after the war. (U.S.D.A. Circular No. 670, 1943).

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Editorial

KEEP MEDICINE FREE

The three fundamentals of a doctor's life are science, economics and humanitarianism. There is a growing science to be followed, a living to make, and a society to be served. As medicine has developed into its present intensive stage, all three of these elements have individually shared in it. Science never was harder to follow. Making a living has become more difficult because of a higher living standard. The demand for increasing medical service is obvious. Whereas in years past a "crisis" was rare, it is now exceptional ever to be without one. Today, a "crisis attitude" exists in science and in medical economics,—in the former because of the rapid pace of discoveries, and in the latter because of the threat of controlled practice.

Those among the laity who desire controlled medicine consist of, (a) those who feel that the cost of medical care has become unfairly high, (b) those who are essentially "planners" with a socialistic leaning and, (c) those who have accepted socialistic propaganda as it applies to medicine without due criticism. Both good and bad doctors will admit that, as non-producers, their services bring them a larger net in comparison with their gross than most businesses, and with fewer variables. Not all doctors oppose the various forms of controlled medicine but among those who do there is the feeling that a controlled system of practice results in a poorer service to the public. The writer is in accord with this belief. The public must be protected from easy fallacies. The public knows that medical propaganda against insurance medicine is stiffening, and often assumes that its object is solely to protect the incomes of doctors. They know that medicine has made remarkable progress in the past quarter century and appreciate this, but they are divided upon the issue of controlled practice. Although the public is almost unanimous in its admiration for medical scientific progress, it gives unqualified liking only to the general practitioner, who, in spite of his necessary scientific limitations, is the only man who has been apotheosized. How can the success of medicine be measured, if not by the degree of esteem in which it is held by the public?

We have been submerged by suggestions for improving the attitude of the public. The obvious formula would be,—reasonable fees in line with the investment and the service rendered, scholarship consistent with our powers, and public service immune to unionism. This formula is based on common sense, but that may be the very reason why it could prove weak in action. It is only the academic and the sophisticated and the logical who have common sense. The public mind deals not in common sense but in impressions and the public intuitively selects its favorites. Remove spontaneity from medicine and there is essentially nothing left.

Remove spontaneity, and soon the great men of our race will avoid entering the profession. This is a more important consideration than would at first appear. In medical history there are approximately one hundred men who showed the rest of us the way. Many of them almost starved, some suffered ostracism, but all of them went into medicine for a life, not a living. Will they continue to take up medicine under conditions of outside control? The writer believes that they will not, and that one of the easiest ways to keep them out is to accept insurance medicine in almost any of its forms.

So long as medicine is progressive, it will survive, but, in the long run, it will retrogress without the periodic stimulation of these masters. Without them, no matter how socialized medicine should be, it will become an increasingly poorer service. Outside authority will ruin spontaneity. If possible we ought to keep medicine free, using all the legitimate means at the disposal of a great and ancient profession. At the moment there is the feeling that we in the United States have the danger of state medicine fairly well under control. Yet, England is about ready to promote greater socialism in medicine, even beyond panel practice. Canada seems certain to accept panel practice very soon. The Beveridge plan is not without inherent attraction to the public elsewhere. The tidal wave of socialism has reached our Atlantic shores. How wet are we going to get?

Book Reviews

Specialties in Medical Practice. Edited by Edgar Van Nuys Allen, with a foreword by Donald C. Balfour. Additions and renewal pages to loose-leaf system. New York and Edinburgh, Thomas Nelson and Sons, 1943.

The first set of renewal pages to this well-received system originally published in 1940 consists of 270 new text pages, two new color plates and an enlarged index. The recent advances in most of the medical specialties are covered fairly well. A valuable inclusion is a table summarizing the signs and symptoms of early vitamin deficiency states.

Chapter 7 has been entirely revised by Don King and is concerned with Orthopedic Surgery. The illustrations are excellent, but in certain instances such as acute osteomyelitis, the text seems somewhat meager. On the whole it is an excellent short review of Orthopedic Surgery. Chapter 13, Minor Surgery, by W. Kenneth Jennings makes its first appearance and is quite satisfactory. The section on fractures is filled with good illustrations and methods of treatment are standard. The paragraphs on peripheral vascular disease are excellent and the section on first aid is also well written.

Fundamentals of Physiology. by Ebert Tokay. Pp. 336. New York, The New Home Library. 1944.

The author is an instructor in physiology at Vassar College. Intended primarily for the layman, the book he has written may serve well as a text for a college course in physiology. In simple language and clear style, the book commences with the general principles of physiology and the organization of the body and then proceeds to discuss the various systems, such as the respiratory and digestive, in more detail. Technical terms, when used, are fairly well defined. A series of 149 original drawings illustrate the text matter. These, for the most part, are helpful but unfortunately some are poorly reproduced.

Vitamins and Hormones, Volume I. Edited by R. S. Harris and K. V. Thimann. Pp. 452. (\$6.50) New York, Academic Press, Inc., 1943.

This book is the first of a series of reference volumes summarizing the current research effort on the chemistry and physiology of vitamins and hormones.

There are ten separate articles on widely separated topics. In view of the highly technical nature of the separate discussions, one must have a broad interest to encompass any considerable portion of any two articles in this book. Therefore this book is obviously intended as a reference work. This intended organization of future volumes has not been made public but one might question the association of subjects in Volume I. For example, an excellent article on the intimate chemistry of compounds from the adrenal cortex is present in the same volume with a discussion of growth factors for protozoa, the significance of the vitamin content of tissues, and the physiology of antipernicious anemia material. Despite this minor criticism this valuable book should be available to all who are doing fundamental research on the vitamins or hormones. The chapter on physical methods for the identification and assay of vitamins and hormones is especially to be recommended as an excellent presentation and evaluation of current available techniques.

Other chapters deal with the chemistry and dietary

significance of choline, the appraisal of nutritional states, photoreceptor function of carotenoids and vitamins A, intermediate metabolism of sex hormones, and the chemical and physiological relationship between vitamins and amino acids. Readers will look forward to succeeding volumes of this valuable work. It is to be hoped that the future essayists will follow the example of their predecessors in Volume I and not become too absorbed in the task of recording facts to point out where knowledge is incomplete.

Textbook of Biochemistry. By Benjamin Harrow, 3rd edition, pp. 536, (\$4.00), Philadelphia and London, W. B. Saunders Co., 1943.

The first edition of this book appeared in 1938. That a third edition should be brought out within five years is indicative of both the rapid advances being made in biochemistry and the popularity of the book. The present edition is one hundred pages longer than the second. To keep future editions within the confines of the present size, and still cover new material, it would be well to sacrifice certain sections. Curtailment or deletion of parts of the book dealing with foods, vitamins and endocrinology would be advisable since these subjects are discussed adequately in texts on nutrition, physiology and endocrinology.

The book is concise and readable. Most of the illustrations are good; a few, however, are disappointing for a textbook of biochemistry. (For example what relation has figure 51 to the text material?) Physical chemistry is perhaps treated at insufficient length but this no doubt is a matter of opinion of what a textbook of biochemistry should cover. To the brief discussion of the nature of trypsin and pepsin, a note should be appended to inform the reader that these enzymes in crystalline form do not behave the same as they do in digestive secretion.

The book will give the medical student nearly all he needs to know for his course in biochemistry and is also an excellent refresher for the doctor. It is recommended for its down-to-earth treatment of the subject.

Abstracts of Current Literature

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CLINICAL MEDICINE

STOMACH

LAW, H. W.: *Hernia of the stomach through the right side of the diaphragm.* (Canadian Med. Assoc. J., V. 50, P. 62, January 1944.)

Left-sided diaphragmatic herniation of the stomach

has been known to result from trauma. However, it has generally been believed that right-sided diaphragmatic hernia is due only to some congenital malformation. The present case would tend to dispel this conception. The patient was a 36 year old army mechanic who presented a history which led to the conclusion

that his right-sided hernia was traumatic in origin.—
F. E. St. George.

BOWEL

DANIELS, E. I.: *Ano-rectal suppurative disease and ano-rectal fistula.* (Canad. Med. Assoc. J., V. 50, P. 147, February 1944.)

The successful correction of suppurative affections of the ano-rectal region depends upon a thorough and modern knowledge of the anatomy of the region. The author has been able to correct over 400 acute or chronic peri-rectal suppurative cases without resultant incontinence. The anatomy is described. While the usual organisms found were staph. aureus and B. pyocyaneus, only one of the entire series had a true tuberculous infection. Any two of three factors are necessary for development of peri-ano-rectal suppuration: 1. Liquid or mushy stools lodging in crypts of Morgagni. 2. Presence of rudimentary racemose multilocular glands in the peri-anal or peri-rectal spaces; and 3. Low resistance to infection. The frequency and nature of the various types (or situations) of abscesses are discussed. In diagnosis, palpation is best and probing or dye injection into chronic fistulous tracts is to be deprecated. In treatment, immediate drainage is required for the acute abscess, and this is done by the "open de-roofing method", using "saddle anaesthesia". All chronic tracts are completely removed, and all operations are done in one stage. Packing is never used and bowel function is not altered.—
Wm. D. Beamer.

PEMBERTON, J. de J., AND BRINDLEY, G. V.: *Tuberculosis of the rectum: report of case.* (Proc. Staff Meet. Mayo Clinic, V. 19, P. 46, January 26, 1944.)

Tuberculosis of the rectum is rare. The caseous or ulcerative type is secondary to tuberculosis elsewhere in the body and is commoner than the noncaseous or hyperplastic type which is primary in nature. The hyperplastic lesion usually occurs in the ileocecal valve and cecum; extremely few have been reported occurring in the rectum. The case history of a 41 year old male who had the rectum resected is given; on the basis of microscopic appearance and the exclusion of other possibilities, the diagnosis of primary hyperplastic tuberculosis was made.—I. M. Theone.

BURROWS, R.: *Studies on intestinal parasites of mental patients.* (Am. J. Hygiene, V. 38, P. 293, November 1943.)

Anal swabs were made in 1,383 patients and more than 3000 stool specimens taken from 2,055 patients who were all inmates of the South Carolina State Hospital. The staff members of the mental hospital were also examined, as were also the soil, walls, doorknobs, furniture, toilet seats, etc. The incidence of infestation by intestinal parasites was higher in mental cases than in the general state population. The longer the confinement to the mental hospital, the greater was the intensity of the infestation as well as the number of parasitic species. The more severe mental cases were more heavily parasitized and the staff members

attending these patients were likewise more parasitized.—
F. X. Chockley.

MILLIGAN, E. T. C.: *Functional disease of rectum and colon.* (Lancet, 245 (6253): P. 29, 1943.)

"Rehabilitation" is discussed. Of 3 methods (the strainless daily-habit rhythm, the response to the conscious call, and aperient addiction) only the first gave satisfactory emptying of the bowel and satisfaction of the mind.—Courtesy Biological Abstracts.

PANCREAS

KENNEDY, R. L. J. AND BOGGENSTROSS, A. H.: *Fibrocystic disease of the pancreas.* (Proc. Staff Meet. Mayo Clinic, V. 18, P. 487, December 15, 1943.)

Fibrocystic disease of the pancreas in children has many of the features of coeliac disease:—intolerance to fat and carbohydrate, foamy light-colored foul-smelling stools, and failure to gain in weight and height. Unlike cases of coeliac disease, in fibrocystic disease of the pancreas there are also chronic bronchial and pulmonary symptoms which may focus attention on the respiratory tract and cause the true nature of the disease to be overlooked. Duodenal contents are without tryptic activity and diet therapy is ineffective. Life expectancy is a matter of months or a few years. Familial tendency is indicated, but not proved. The greatest age attained in all reported cases is 14 years. Etiology is unknown. Congenital obstruction of the pancreatic secretion and retrograde degeneration may be the essential factor. Some believe that a deficiency in vitamin A plays an important role. No therapeutic measures have as yet been found. The case histories and pathology reports of 4 patients are given; an addendum on two additional cases is also included.—
I. M. Theone.

NAFFZIGER, H. C. AND MCCORKLE, H. J.: *The recognition and management of acute trauma of the pancreas.* (Ann. Surg., V. 18, P. 594, October 1943.)

Damage to the pancreas following traumatic injuries to the abdomen are usually masked by other symptoms. Pancreatic damage resulting from trauma has been detected by the authors by determining the levels of blood serum amylase. They believe that values above the normal are due to absorption of amylase from the peritoneal cavity or from interstitial spaces into which pancreatic juice has leaked. When pancreatic damage of this origin is found, food should be withheld from the patient in order to reduce the secretion of the pancreatic acini to the minimum.—
G. Klenner.

LIVER AND GALLBLADDER

BEAMER, WM. D.: *Biliary drainage by duodenal intubation.* (Med. Clin. N. Amer., P. 1659, November 1943.)

A brief history of duodenal intubation and drainage is given. The technic of passing the tube into the stomach, thence into the duodenum is described. Particular attention is called to necessity of the patient being at perfect ease and understanding the procedure.

Some simple expedients for encouraging duodenal entry are mentioned. Specimens are obtained best for diagnostic purposes when a proteose solution (Bactoprotone) is used. Magnesium sulfate-peptone solution is successful in about 70 per cent of all drainages. Pava-trine has yielded fairly good results but confuses the specimens. Emptying of the gall bladder is favored by an initial high tonus, and this may be expected when the gall bladder is well filled. However, a highly spastic sphincter of Oddi may interfere with drainage. The bile fractions are noted as to color and clarity first, then examined microscopically for diagnostic epithelium, pus, blood, and crystals, as well as bacteria and parasites. Roentgen study should be performed simultaneously with the biliary drainage. Only by duodenal intubation can the process of therapy in biliary tract disease be followed satisfactorily.—Win. D. Beamer.

DESSAU, F. J.: *The incidence of gallstones in the higher age groups.* (*New England J. Med.*, V. 229, P. 464, 1943.)

In the Long Island Hospital, Boston, there were 3242 post mortems performed during the years 1900 to 1942 inclusive. Of these, 2791 were performed on people over 40 years of age. The incidence of gallstones was found to increase with age. Cholecystitis without gallstones was present in 2.5 per cent of the autopsied patients. Cholecystitis associated with cholelithiasis was seen in 42 per cent of the males and 34 per cent of the females. The incidence of gallstones was greater in the years 1923 to 1942 than 1900 to 1923. There was a gradual decrease in the sex ratio difference; in later years it has been approximately only twice as prevalent in women than men.—D. A. Wocker.

SCHWYZER, A.: *White bile.* (*Minnesota Med.*, V. 26, P. 955, November 1943.)

The so-called "white bile" seen by the surgeon in cases of bile-duct obstruction usually is not due to infection but to obstruction of bile flow. The "white bile" is not a secretion of the hepatic cells but of the glandular cells of the bile ducts. The white bile actually is not white but colorless and is devoid of bile acids and bile pigments. A colorless secretion from the hepatic cells is found only when the liver is extremely damaged but the ducts are not obstructed. Usually, however, any secretion from the liver cells is colorless. After release of the obstruction normally colored bile should begin to flow within forty-eight hours. Schwyzer discusses nine cases from his experience, excluding hydrops of the gall-bladder.—G. Klenner.

ULCER

ROTHER, H.: *Incidence of gastric and duodenal ulcers in war.* (*Deutsch. med. Wochenschr.*, V. 67, P. 810, 1941.)

Results of 7,488 studies over 3 years, 1937-40, are reported. A considerable periodicity was noted, with a maximum incidence in winter and without marked peaks in spring or fall. The total number of examina-

tions increased somewhat during the last 2 (war) years and the percentage of positive findings increased. The frequency of gastric ulcers increased relatively more than that of duodenal ulcers in the last year: the percentage of gastric ulcers, in terms of total ulcers found, was 17.9 for 1937/38, 11.9 for 1938/39 and 27.4 for 1939/40.—Courtesy Biological Abstracts.

FOWLER, R. H.: *External trauma and peptic ulcer.* (*Indust. Med.*, V. 12, P. 614, 1943.)

Peptic ulcer as the result of blunt traumatism has an incidence of 0.6 per cent. The question of the traumatic origin of an ulcer has been raised on many occasions in industrial compensation cases. Fowler presents a number of conditions which must be met in order that a peptic ulcer may be recognized as traumatic in origin.—G. Klenner.

SURGERY

PRIESTLEY, J. T., THOMPSON, L., AND SEALY, W. B.: *Bacteriologic aspects of gastric content in presence of surgical lesions of the stomach and duodenum.* (*Proc. Staff Meet. Mayo Clinic*, V. 19, P. 1, January 12, 1944.)

While the contents of the normal fasting stomach are usually sterile, bacteria may be present in association with certain gastric lesions. The bacteria normally present in the mouth and oesophagus, and those ingested with food, are destroyed by the acid of the gastric juice. This probably also accounts for the bacteria-free condition of the contents of the duodenum and upper jejunum.

Bacteriologic examination was made of the gastric contents of 41 patients subjected to operation (39 for gastric resection and two for gastroenterostomy). Acidity determinations of the gastric contents were also made. No organisms were found in 24 cases and one or more organisms in 17. Organisms were rarely recovered from gastric content if the total acidity of juice secreted prior to operation (in response to a Ewald test meal) was more than 40 clinical units. Only 4 out of 22 duodenal ulcer cases showed organisms present in the gastric contents while 6 out of 7 gastric ulcer cases and each of 5 cases of malignant gastric lesion showed organisms.

From the foregoing the authors conclude that every case of malignant gastric lesion or gastric ulcer must be regarded by the surgeon as one where infection already exists. Danger from infection in duodenal ulcer surgery is seldom serious.—I. M. Theone.

EXPERIMENTAL MEDICINE

PHYSIOLOGY SECRETION

SPEALMAN, C. R.: *The volume flow of resting salivary secretion.* (*Amer. J. Physiol.*, V. 139, P. 225, 1943.)

The total salivary production was collected by allowing the saliva to drain into a 50 cc beaker over a 5 minute period after the establishment of constant drainage from the mouth. Using the method for determining the resting volume flow of salivary secretion, evidence was obtained that the mean of a

sufficient number of determinations represented a value which was reproducible and characteristic of the individual. The distribution of the mean of 2 values of a limited number of subjects was skewed. The modal value was about 0.24 cc per minute. The lowest mean of values obtained was 0.08 cc per minute and the highest 0.88 cc per minute.—C. R. Speakman.

PHYSIOLOGY MOTILITY

QUIGLEY, J. P., BARON, H. J., READ, M. R., AND BRAFMAN, B. L.: *Evidence that body irritations or emotions retard gastric evacuation, not by producing pylorospasm but by depressing gastric motility.* (J. Clin. Invest., V. 22, P. 839, Nov. 1943.)

Supposed evidence that decreased gastric emptying is due to pylorospasm incident to viscerovisceral or somatovisceral reflexes has accumulated in the literature from three main sources: clinical, roentgenological, and experimental.

Clinical diagnosis of pylorospasm depends largely on support from X-ray studies. But roentgenological studies have usually assumed that the non-visualizing sphincter is either closed or in spasm, which is erroneous. When the sphincter is actually visualized and pylorospasm is distinguished from certain pathological conditions (edema, scar contractures) it has been found that the sphincter is open most of the time, closing intermittently only for brief intervals; and that in many cases of food retention the pylorus is found to be patent.

Numerous studies have gradually established the views that gaster and sphincter behave, not antagonistically as formerly believed, but similarly and as a unit; and that gastric evacuation is dependent largely on gastric peristalsis and not on sphincteric activity. However, past experiments by others in anesthetized animals have led to the conclusion that pylorospasm is induced by visceral and somatic reflexes. The present series of experiments analyzes results obtained from trained unanesthetized dogs, with improved methods of studying sphincteric activity (pyloric diaphragm, triple-balloon technique, X-ray).

Nervous states, peripheral nerve stimulation and visceral distention produced a consistent loss of tone and motility of the antrum, sphincter and bulb. Supradiaphragmatic vagotomy will not destroy the inhibiting effects of distention. Increase in sphincteric tone and motility were obtained only by placing 0.4 per cent hydrochloric acid in the duodenal bulb, by gastric distension, and during nausea, retching and vomiting.

These results yield little support to the claim that pylorospasm is produced by emotional states or noxious stimuli.—J. L. Garcia-Oller.

ABSORPTION

RAMMELKAMP, C. H. AND HELM, J. D.: *Studies on the absorption of penicillin from the stomach.* (Proc. Soc. Exp. Biol. Med., V. 54, P. 324, December 1944.)

Penicillin is absorbed poorly when administered by mouth. This is due to inactivation by the gastric juice. The acid rather than pepsin is responsible. Saliva, bile and succus entericus do not inactivate the drug. Ab-

sorption of penicillin administered by mouth occurred in patients with pernicious anemia.

These experiments show that penicillin should not be given by mouth. The use of enteric coated capsules is not likely to prove effective since the bacteria of the lower intestine may destroy the penicillin unless the capsule is dissolved in the upper intestine.—M. H. F. Friedman.

PATHOLOGY

CHAIKOFF, I. L., ENTENMAN, E., RINEHART, J. F., AND REICHERT, F. L.: *Development of cirrhosis in the liver of dogs deprived of both pituitary and thyroid glands.* (Proc. Soc. Exper. Biol. Med., V. 54, P. 170, November 1943.)

Dogs deprived of both the pituitary and thyroid glands showed a high blood lipid concentration. Although the diet of such dogs was adequate with respect to caloric value, proteins, salts and vitamins, and was not high in fat, the livers of the dogs showed varying stages of cirrhosis. Fat was found distributed in the liver cells both in small and large droplets. Such a high fat content of the liver (11 to 52 per cent) was not found in dogs subjected to thyroidectomy alone.—M. H. F. Friedman.

BROWN, CLARK E.: *Dietary ulcers of the esophagus of the rat.* (Amer. J. Path., V. 19, P. 785, 1943.)

Of 17 white rats of the Osborne-Mendel strain between 2 and 3 months of age fed a diet of unpolished Texas rice and cottonseed oil for 6 months or longer, 12 developed hyperkeratosis of the esophageal mucosa and in 8 of these there was definite ulceration, sometimes of the penetrating type. Another group of 16 rats similar in age, sex and weight were fed the same deficient diet for 5 months. Then the diet was supplemented by synthetic vitamins and a salt mixture for one month and the rats were sacrificed. Only 4 showed hyperkeratosis of the esophageal mucosa and there was no ulceration. Thus the lesions appear to be primarily dietary in origin.—Courtesy Biological Abstracts.

KRAKOWER, C., HOFFMAN, W. A., AND AXTMAYER, J. H.: *Portal-systemic collateral veins in the guinea-pig with schistosomal cirrhosis of the liver, and a discussion of congestive splenomegaly.* (Arch. Path., V. 36, P. 39, 1943.)

Previous descriptions of portal-systemic venous anastomoses in laboratory animals were based on injections at maximum pressure of portal vein and/or inferior vena cava in normal animals, or by the production of portal hypertension through various operative methods, entailing the formation of peritoneal adhesions and new vascular pathways. The anastomoses observed in the intact guinea-pig with cirrhosis of the liver produced by experimental infection with *Schistosoma mansoni* were described. They fell into 2 groups: (1) The minor anastomoses, viz., those that were periesophageal, those in the falciform ligament, in the hemorrhoidal system, and in the distal portion of the inferior mesenteric vein; nothing, however, resembling esophageal, epigastric or hemorrhoidal varices

was noted. (2) The major anastomoses, necessitated chiefly by the absence of parietal peritoneal fixation of duodenum, pancreas and colon (as in rodents), occurred in the porto-caval triangle and the lienopancreatic-mesoduodenal areas and were made up of large vessels arising from the superior and inferior mesenteric and gastro-splenic veins. These emptied into the large systemic veins. Congestion splenomegaly (Banti's type) was not obtained. The failure to produce this condition in laboratory animals under natural or experimental conditions is attributed to the fact that in small laboratory animals with portal obstruction, the smaller volumes of portal blood can be shunted more efficiently and with the maintenance of lower pressure, in the absence of hydrostatic pressure due to gravity, through the few, short, direct and indirect anastomoses, larger blood volume, and greater hydrostatic pressure, congestive splenomegaly can occur more readily.—Courtesy Biological Abstracts.

DRAGSTEDT, L. R.: *Some physiologic problems in surgery of the pancreas.* (*Ann. Surg.*, V. 118: 576, October, 1943.)

The author reviews his experiences with various operative procedures upon the pancreas, such as complete removal, occlusion of the ducts, transplantation of the ducts to the exterior, etc. He found that when the pancreas was entirely absent, almost all dogs develop fatty infiltration of the liver. This was found to be counteracted by feeding pancreatic tissue to the dogs. Further study showed that occlusion of the ducts produced fatty livers in 50 per cent of the dogs, and that the alpha and beta cells survived in the islets in these animals, but the acinar tissue was destroyed. Alpha cells in the acinar tissue may exceed the number in the islets; beta cells are found only in the islets. It is probable that the alpha cells secrete a hormone (lipocain) which prevents the deposition of excessive fat in the livers, and when occlusion of the pancreatic ducts is complete, these cells in the acinar tissue are injured while those in the islets are not. Young, and Ham and Haist produce diabetes by destroying the beta cells by anterior hypophysis extracts, but the alpha cells are not injured except in two dogs and only in these two is there extensive fat deposition in the liver. While almost all dogs with total pancreatic fistulas developed ulcer of stomach or duodenum, (unless heavily treated with alkali), only a dozen of over 400 dogs with the pancreas removed developed ulcers. Those with ligated pancreatic ducts occupy a middle position.—Wm. D. Beamer.

METABOLISM AND NUTRITION

KUNSTADTER, R. H. AND NECHELES, H.: *Studies on the effect and mechanism of amphetamine sulfate on weight reduction.* (*Am. J. Med. Sci.*, V. 205, P. 820, June 1943.)

The experiments were undertaken to determine the possible causes for decrease of appetite and loss of weight of obese children resulting from the administration of amphetamine sulfate. Observations were made of the psychic gastric secretion (acidity and volume)

and motility of dogs provided with a double-barreled esophagostomy and a Pavlov pouch. Clinic patients were used also. It was found that the effect of 3-to 5 mgs of amphetamine sulfate on secretion in Pavlov pouch dogs was variable and transient. Gastric motility was suppressed in these dogs very shortly after administration of the drug and this was found to be true in the human as well. In cases where motility was not arrested altogether it was modified so that typical strong hunger contractions did not occur.

The psychic effects noted in children were increased physical activity, increased mental and physical responses and stronger will power. This increased self-discipline was not due to parental policing because when other drugs were given, the children's appetites increased.

The authors conclude that the loss of weight in obese children under this treatment may thus be due to the psychic effects of amphetamine plus the depression of hunger and gastric hunger motility.—R. L. Birdick.

WHITE, E. A., FOY, F. R., AND CERCEO, L. R.: *Essential fatty acid deficiency in the mouse.* (*Proc. Soc. Exp. Biol. Med.*, V. 54, P. 301, Dec. 1943.)

Albino mice kept on a diet free from fat developed symptoms characterized by growth retardation, tail and leg necroses, scaly dermatitis, hematuria and kidney lesions. The earliest symptoms of this Burr and Burr syndrome consisted of a dandruff-like dermatitis and appeared on the 30th to 40th day. The development of the symptoms could be prevented by the inclusion of 10 per cent lard in the diet; similarly the addition of lard to the diet would cure the condition once it had developed.—M. H. F. Friedman.

GOMORI, G., AND GOLDNER, M. G.: *Production of diabetes mellitus in rats with alloxan.* (*Proc. Soc. Exp. Biol. Med.*, V. 54, P. 287, Dec. 1943.)

Forty rats were given single intraperitoneal injections of alloxan, 200 mg per kilogram body weight, as a 5 per cent solution freshly prepared. The animals were kept in metabolism cages and groups sacrificed at different time intervals. Urine was analyzed for sugar and ketone bodies, blood for sugar, and histological sections were made of the pancreas, liver and kidneys.

Diabetes mellitus was produced by the alloxan. Polyuria was common. A 30 per cent loss in weight was recorded. The pancreas showed necrosis and complete disappearance of the beta cells. The ducts and the acinar parenchyma showed no changes.—M. H. F. Friedman.

MISCELLANEOUS

HOLLING, H. E., MCARDLE, B. AND TROTTER, W. R.: *Prevention of seasickness by drugs.* (*Lancet*, V. 1, P. 127, January 22, 1944.)

Although seasickness is not so great a problem in the fighting forces as might be supposed, it is desirable to prevent it in all susceptible cases. The best method is by trying various drugs along with dummy tablets in small groups for short voyages in rough seas. Several

sedative drugs, drugs of the belladonna group, and three proprietary preparations were tested on military personnel. Of all these drugs, hyoscine gave the highest percentage of "susceptibles protected." The only undesirable side-effect is dryness of the mouth. It appears that some related drug which will not decrease salivation would be very useful.—William D. Beamer.

BALLON, OSCAR URTEAGA: *Discussion on the pathogenesis of some types of jaundice with special reference to hemolytic jaundice and to chronic mountain sickness.* (An. Fac. Cienc. Med., V, 25, P. 89, 1942.)

It is suggested that a type of jaundice exists dependent upon increased threshold for excretion of bilirubin. In hemolytic jaundice, such elevated threshold could be regarded as a pigment from destroyed red cells. A similar compensatory device should be considered as a possibility in explaining the elevated bilirubin level and the polycythemia in chronic mountain sickness.—Courtesy Biological Abstracts.

HOWE, H. A. AND BODIAN, D.: *A note on the penetration of poliomyelitis virus from the gastrointestinal tract in the chimpanzee.* (J. Ped., V, 21, P. 713, 1942.)

Active virus from human stools was given to a chimpanzee by stomach tube. On the 4th day following first inoculation the animal was delirious—fever 109° F. Extremities showed spasms, back stiff. Extensive studies of the brain, medulla, ganglia, spinal cord at different levels from cervical to sacral and intestines showed no pathology except in the celiac ganglia and the right sympathetic chain. The latter showed some perivascular cuffing in the thoracic portion and a large area of lymphocytic infiltration in one of the lumbar ganglia. The celiac ganglia contained many areas of infiltration and cuffing adjacent to the efferent nerves. The authors conclude that poliomyelitis virus may reach the central nervous system from the gut via the abdominal sympathetics.—Courtesy Biological Abstracts.

SHWACHMAN, H., FARBEN, S., AND MADDOCK, C. L.: *Pancreatic function and disease in early life III. Methods of analyzing pancreatic enzyme activity.* (Am. J. Dis. Child., 66, 418, October 1943.)

Incubations were carried out with Levin tubes or catheters (No. 10 or 12 French depending on the patient's age), and checked for position fluoroscopically. Collection was by gentle aspiration, with immediate refrigeration of specimens until analysis. pH was determined colorimetrically. Lipase was done essentially by the method of Willstätter et al., using a one hour incubation period. The substrate was olive oil, with albumin and CaCl₂ in a glycine buffer of pH 8.9. Fatty acids were titrated with KOH. Although results varied widely in a given patient, and with two preparations of olive oil emulsion, this was not felt to impair the validity of the test.

Trypsin was determined in the Ostwald viscosimeter with a 3% phosphate-buffered gelatin substrate, using a one hour incubation period and several determinations to establish the time required for a constant propor-

tionate decrease in viscosity. Variations in the gelatin are held to account for much of the variability in results. A large drop in activity was noted in specimens kept at room temperature for 24 hours. For rapid, approximate determinations, the authors used a gelatin film, noting the concentration of specimen required to liquefy a spot under standard conditions. A third method described was a modification of that of Anderson and Early which determines the maximum dilution of a specimen preventing refrigerator solidification of a standard gelatin solution, whose make-up is given. The first and last methods showed correlation close enough for clinical dependability.

Amylase was determined viscosimetrically essentially according to Davison. The substrate was soluble starch in an acetate buffer at pH 6.8.—B. C. Riggs.

RAISKY, H. A.: *Gastrophotography in natural colors in conjunction with gastroscopy.* (Am. J. Med. Sci., 206, 618, Nov. 1943.)

The author employed the Gastro-Photocamera and took his pictures on Kodachrome film. The camera was placed into the stomach after gastroscopic observation had been performed, and the position of the lesion to be photographed had been determined. This study consists of observations in forty-one patients with comparison of the findings of both of the above methods as well as by examination of surgical specimens. In 63.4% of the cases the photographs revealed identical findings with those of the gastroscopist. The author feels that the added use of the Gastro-Photocamera or some similar apparatus is of value in that a permanent record of the findings will be available, that the findings of different observers may be compared, and that this "enhances the endoscopic examination on one hand, and illustrates its limitations on the other."—I. J. Pincus.

LIGHT, J. S. AND HODES, H. L.: *Studies on epidemic diarrhea of the new-born: isolation of a filtrable agent causing diarrhea in calves.* (Am. J. Pub. Health, 33, 1451, Dec. 1943.)

This report gives the results of studies of 6 separate epidemics of diarrhea of the new-born occurring in 3 hospitals in the Baltimore-Washington area during a period of 2 years. Stool cultures were uniformly negative for known diarrhea-producing organisms.

In the first two epidemics stools, blood, and nasal washings from a number of the babies were injected by various routes into a variety of the smaller animals, without producing any definite disease. In the subsequent 4 epidemics stools of affected babies were given intranasally to Guernsey calves. A bloody, mucoid diarrhea resulted in the inoculated animals. Successive calf passages were made. The disease was produced in a total of 84 calves. The infecting dose was 1 ml. of unfiltered material or 8 ml. of filtered material. Stools from normal calves did not produce diarrhea. No organism was cultured from the filtered stools.

The authors state that their evidence suggests that the agent may be a cause of epidemic diarrhea of the new-born, but admit it is not conclusive.—G. P. Blundell.

Inhibition of Peptic Activity In The Treatment of Peptic Ulcer

By

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AND

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PEPTIC ulcer of the gastro-intestinal tract has long been recognized as being due to the action of gastric juice rich in hydrochloric acid and pepsin (1, 2, 3). However, in discussing the pathogenesis of gastroduodenal ulcer, most authors emphasized primarily the role of acid to such an extent that the pepsin factor was almost forgotten. Due to various observations made in recent years, however, the significance of the pepsin factor in the development of gastroduodenal ulcer has received renewed attention. Thus it was found that by perfusing segments of the gastro-intestinal tract with acid and pepsin more severe ulcers were produced than with perfusion of acid alone (4). Furthermore, it has been stressed that ulceration of the gastro-intestinal tract in animals has never been produced by the application of physiological concentrations of hydrochloric acid in the absence of pepsin (5). Finally it has been shown that the histamine stimulated gastric juice is not only strongly acid but also rich in pepsin (6, 7, 8).

The significance of the pepsin factor has recently been ably demonstrated by Shoch and Fogelson (9) who were able to keep dogs alive (in whom ulcers were produced by daily histamine injections) for a much longer period of time when the peptic activity of the gastric juice was inactivated without altering its pH. These authors therefore questioned the validity of the name "acid ulcers" for ulcers produced by the daily injection of histamine.

Because of the above observation it seems logical that in the treatment of peptic ulcer not only the acid but also the pepsin factor should be considered; and that in prescribing drugs for the treatment of ulcer, not only their antacid but also their antipepsin activity should be evaluated. Furthermore, it appears desirable to determine whether in the treatment of peptic ulcer a substance which has little or no antacid effect would still have antipeptic activity and be clinically of therapeutic value. The latter thought arises from Shoch and Fogelson's observations (9, 10) that sodium lauryl sulfate inhibited the peptic activity of the gastric juice without altering its pH.

Since the above results clearly point to the importance of pepsin in the genesis and chronicity of gastroduodenal ulceration, it was planned to determine the effect of certain antacids on the peptic activity of the gastric contents in man. We also planned to determine whether sodium lauryl sulfate, while leaving

the pH unaltered, would inhibit the peptic activity more completely than the other antacids, and whether it was an effective substance in the treatment of peptic ulcer patients.

METHOD AND MATERIAL

Patients who were admitted to Cook County Hospital as peptic ulcers, and in whom this diagnosis was confirmed by clinical and x-ray findings, were used for this study. The following procedure was carried out: A Rehfuess tube was introduced into the stomach of the fasting patient and an attempt was made to aspirate the entire gastric contents. Then, with the tube in situ, the patient ate four Uneda crackers and drank one glass (200 cc.) of water. Samples of gastric juice were aspirated every fifteen minutes for two hours (or less if no juice was obtained at an earlier period). A total of nine specimens of gastric juice were thus obtained from most of the patients. The pH* and peptic activity** were determined in each of the specimens. On succeeding days the same procedure was repeated but the patient received, shortly after taking the crackers and water, either (a) one capsule (100 mg.) of sodium lauryl sulfate, (b) two capsules (100 mg. each) of sodium lauryl sulfate, (c) 2 grams of calcium carbonate, (d) 8 cc. of an aluminum hydroxide preparation, or (e) two tablets of a magnesium hydroxide compound (containing 6 gr. of magnesium hydroxide). In addition, some patients were given one or two capsules of sodium lauryl sulfate respectively, and others two tablets of the magnesium hydroxide immediately following the fourth aspiration, i.e. at hourly intervals. Each patient was tested for five successive days.

To test the efficacy of sodium lauryl sulfate a similar group of patients were given the usual ulcer diet plus one capsule of sodium lauryl sulphate every hour for twelve doses or more depending on the patient's symptoms. These patients were observed during their stay in the hospital and later as out patients in the follow-up Gastro-intestinal Clinic where they were seen once every week. An attempt was made not to give them any other antacid therapy, but tincture of belladonna or phenobarbital was frequently given as supplementary medication.

RESULTS

A. Evaluation of Antacid and Antipeptic Effects.

After the simple test meal it was noted that the pH which was initially 2.8, dropped to 1.5 at the end of

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* From the Departments of Therapeutics and Internal Medicine and the Gastro-intestinal Clinic of the Cook County Hospital and the Department of Internal Medicine, University of Illinois College of Medicine, Chicago, Illinois.

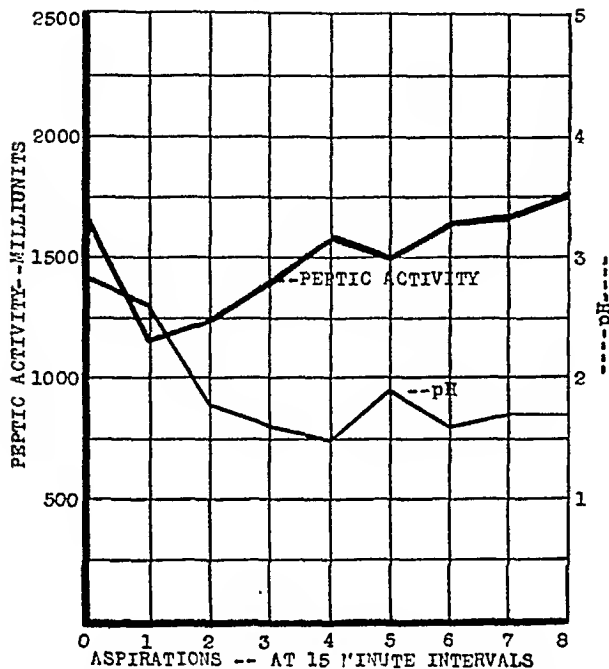
Aided by a grant from the Nutrition Research Laboratories, Chicago.

* pH determined by the Beckman potentiometer.

** Peptic activity determined by the modified Anson-Mirskey¹¹ hemoglobin method.

one hour, rose slightly during the next fifteen minutes and, finally, at the end of two hours was 1.7. The peptic activity which was 1,620 milliunits dropped to 1,150 milliunits at the end of fifteen minutes, but then gradually rose until at the end of two hours it was 1,760 milliunits (Graph 1).

GRAPH I



Curves showing peptic activity and pH after simple test meal.

Following the test meal plus 2 gm. calcium carbonate, the initial pH of 2.9 rose to 5.4 within fifteen minutes. After forty-five minutes, however, it dropped to 2.6 and at the end of two hours it was 1.7. The initial peptic activity which was 1,450 dropped to 710 milliunits within fifteen minutes, but after forty-five minutes it had risen to 1,320, and at the end of two hours the peptic activity was 1,720 milliunits (Graph 2).

Following the addition of 8 cc. of an aluminum hydroxide preparation to the test meal the pH rose from an initial reading of 4.2 to 5.1 within fifteen minutes, but after forty-five minutes it had dropped back to 2.3 and at the end of two hours it was 1.8. The peptic activity which was 1,140 milliunits initially dropped to 650 within fifteen minutes, but after forty-five minutes it had risen to 1,280, and at the end of two hours it was 1,710 milliunits (Graph 3).

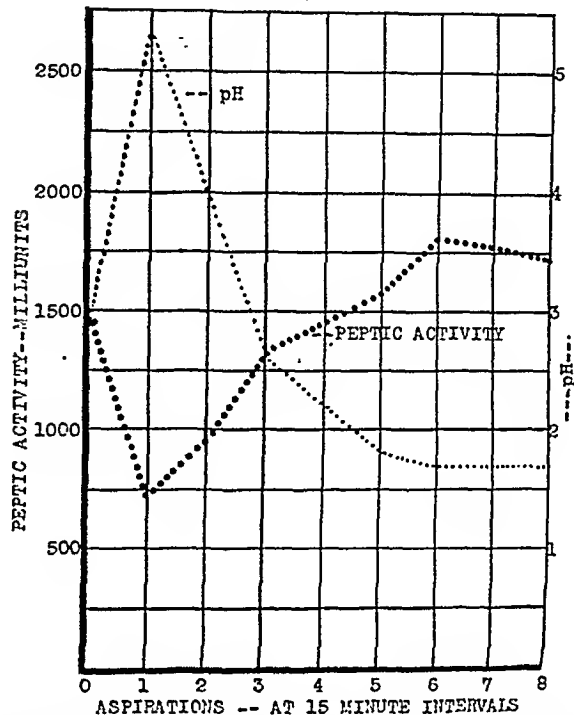
After the test meal plus 6 gr. of magnesium hydroxide the initial pH of 3.5 rose to 4.6 but after one hour it had dropped to 1.4 at which level it remained for the remainder of the examination. The peptic activity which initially was 1,130 milliunits dropped to 591, but after one hour it had risen to 1,440, and at the end of a two-hour period it was 1,763 milliunits (Graph 4).

After the ingestion of the test meal plus one capsule of sodium lauryl sulfate, the pH of 2.6 did not rise but dropped gradually until at the end of two hours it

was 1.7. The pepsin activity, however, which was 1,310 milliunits at the beginning dropped slightly, i.e. to 1,040 milliunits, but then it rose until at the end of two hours it was 2,090 milliunits (Graph 5).

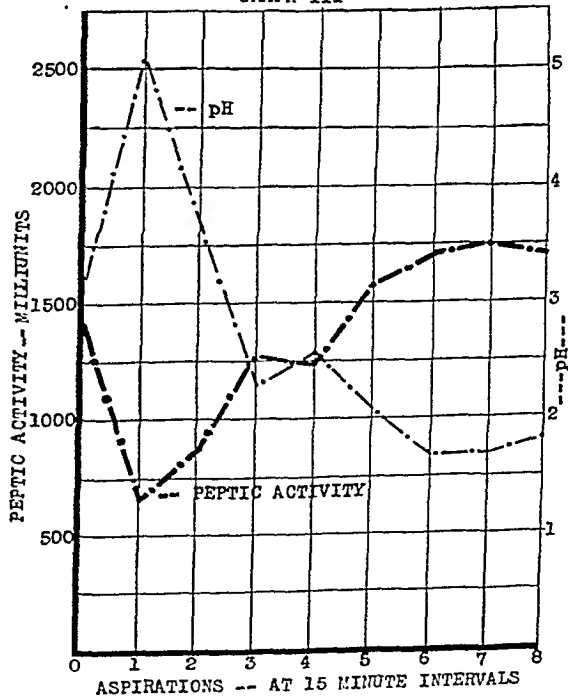
After the test meal plus two capsules of sodium lauryl sulfate the initial pH of 2.8 rose to 3.1, but after

GRAPH II



Curves showing peptic activity and pH following test meal plus calcium carbonate (30 Gm.) taken immediately after ingestion of test meal.

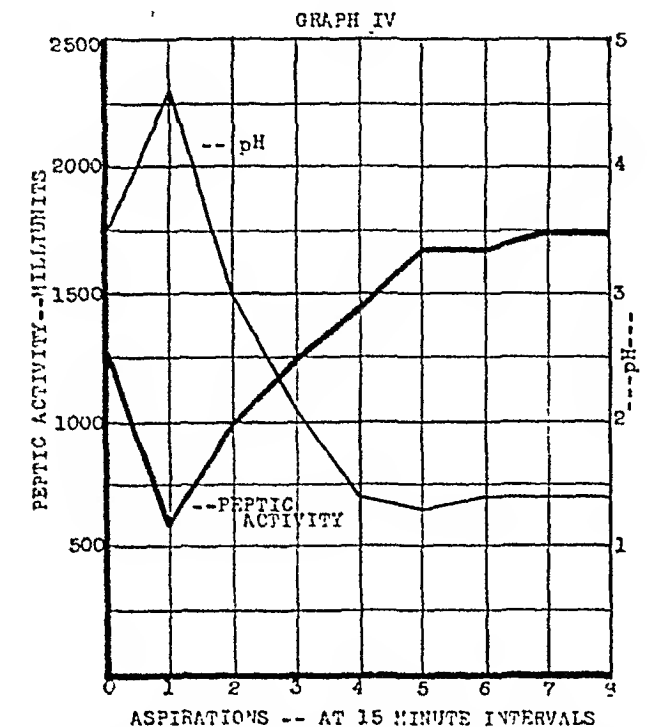
GRAPH III



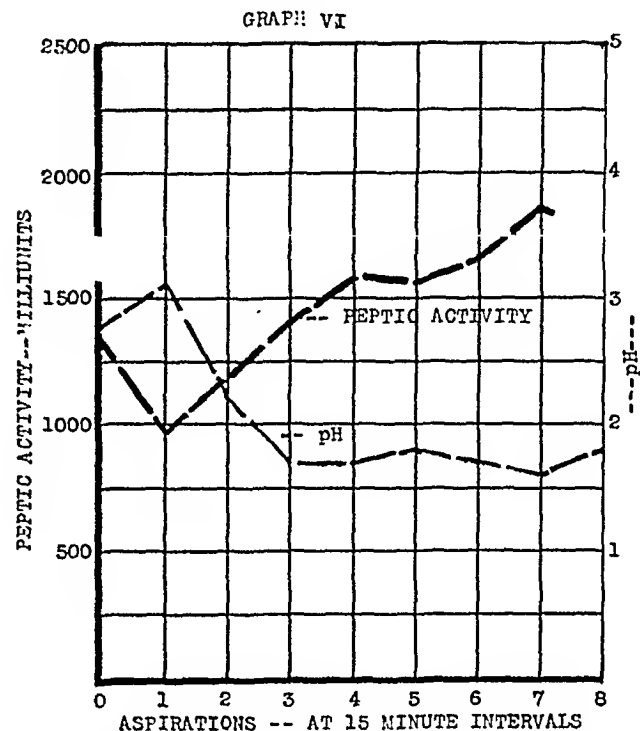
Curves showing peptic activity and pH following test meal plus 8 cc of an aluminum hydroxide preparation taken immediately after ingestion of test meal.

thirty minutes it had dropped to 2.2, and at the end of two hours it was 1.8. The peptic activity which initially was 1,310 milliunits dropped to 970 but after thirty minutes rose to 1,200 and then continued to

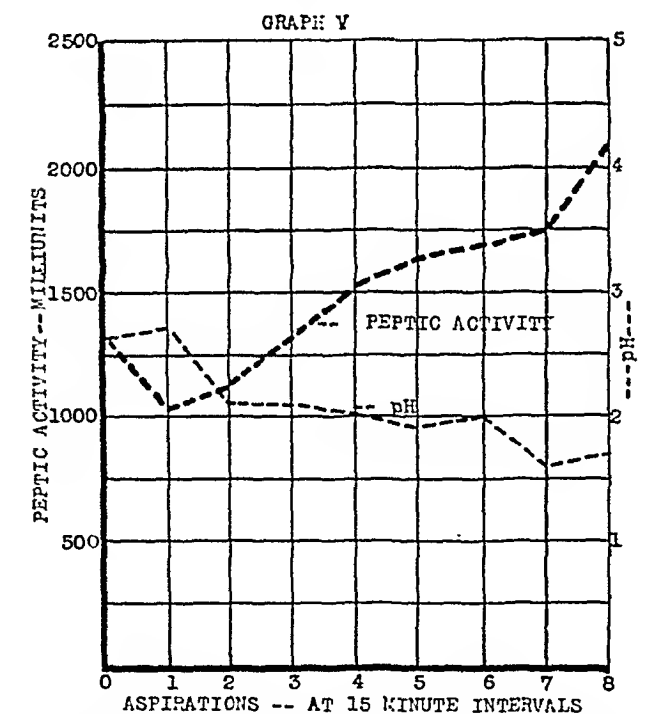
activity were compared following various doses of sodium lauryl sulfate and magnesium hydroxide repeated at hourly intervals. Aspirations were done at half hourly intervals. In these, following the



Curves showing peptic activity and pH following test meal plus 6 gr. of a magnesium hydroxide mixture taken immediately after ingestion of test meal.



Curves showing peptic activity and pH following test meal plus 200 mg. sodium lauryl sulfate taken immediately after ingestion of test meal.



Curves showing peptic activity and pH following test meal plus 100 mg. sodium lauryl sulfate taken immediately after ingestion of test meal.

rise until at the end of two hours it was 1,750 milliunits (Graph 6).

In a small number of patients the pH and peptic

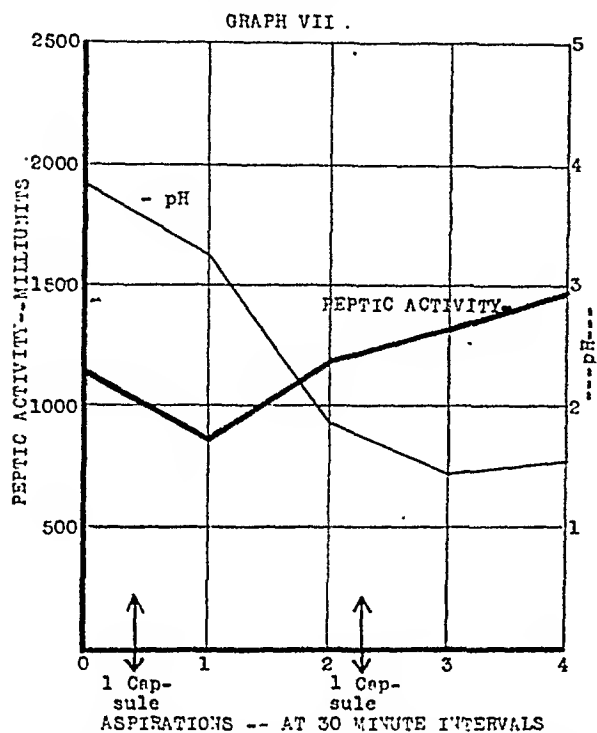
plain test meal, the initial pH of 3.7 continued to drop until at the end of two hours (after the fourth aspiration) it was 1.7. During this time the initial peptic activity of 1,250 milliunits dropped within thirty minutes to 980 but then gradually rose until at the end of two hours it was 1,460 milliunits. Following the test meal plus 100 mgm. of sodium lauryl sulfate taken by the patient immediately after the test meal and 100 mgm. one hour later, the initial pH of 3.75 dropped gradually until at the end of two hours it was 1.55. The peptic activity which was 1,140 milliunits initially, dropped within half an hour to 865 but after one hour it was above its former level and continued to rise in spite of the ingestion of a second dose, until at the end of two hours it was 1,475 milliunits (Graph 7).

After the ingestion of the test meal and 200 mgm. of sodium lauryl sulfate, the pH dropped from an initial level of 3.6 to 3.1 within thirty minutes, and then continued to drop in spite of the ingestion of 200 mgm. of sodium lauryl sulfate after the second aspiration—one hour after the first dose—until at the end of two hours it was 1.85. At the same time the peptic activity which was 1,260 milliunits initially dropped within half an hour to 720, but then began to rise until at the end of two hours it was 1,830 milliunits (Graph 8).

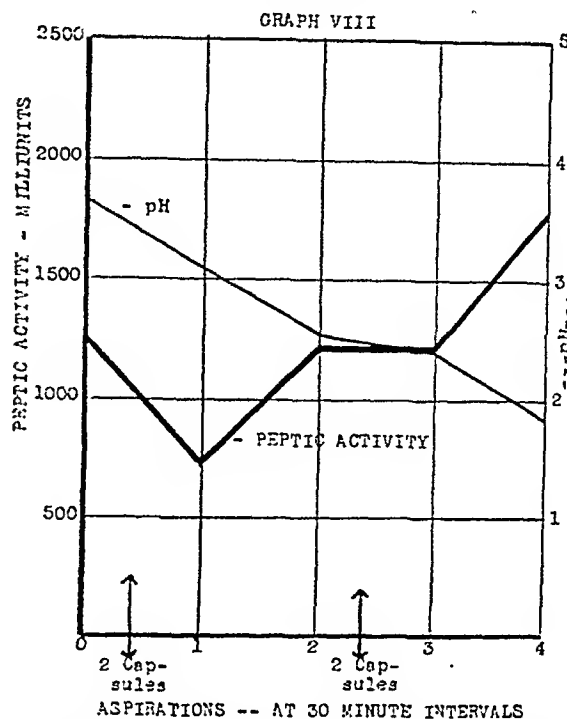
The patients who received 6 gr. of magnesium hydroxide at hourly intervals showed a slightly higher pH within half an hour after the second dose, but at

the end of the two-hour period the pH was down to 1.6. The peptic activity was not influenced by the second dose of magnesium hydroxide inasmuch as it continued to rise uninterruptedly (Graph 9).

num hydroxide preparation and the magnesium hydroxide had the most influence on both the pH and the peptic activity, both causing the greatest rise of the pH and the greatest decrease in the peptic activity



Curves showing peptic activity and pH following test meal plus 1 capsule (100 gm.) sodium lauryl sulfate immediately after ingestion of test meal and a second capsule taken 1 hour later.



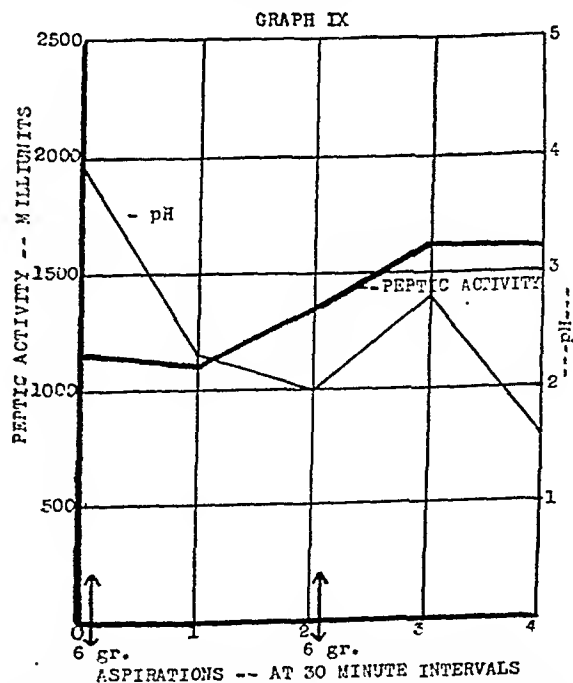
Curves showing peptic activity and pH following test meal plus 2 capsules (200 Gm.) sodium lauryl sulfate immediately after ingestion of test meal and 2 more capsules taken 1 hour later.

B. Evaluation of Clinical Results.

Of the patients who were given sodium lauryl sulfate as the antacid medication during their stay in the hospital, many gradually dropped out soon after leaving the hospital so that we have available data on only twelve patients who were observed from five to fifteen months. These patients would get various degrees of relief as long as they took the sodium lauryl sulfate (100 mgm.) at hourly intervals. The majority of them had to receive tincture of belladonna and phenobarbital as adjuvants. There were no specific symptoms that were particularly relieved by sodium lauryl sulfate. Some patients requested a laxative medication during this time. Several patients who were asked to discontinue the hourly use of sodium lauryl sulfate and take it at two-hour intervals complained of epigastric distress and had to return to the hourly dose.

DISCUSSION

As previously reported (12) and as seen from Graphs 1 to 9 there was a rather slow drop in the pH following the simple test meal until at the end of two hours it had reached the level around which optimum digestion occurs. The peptic activity decreased slightly but then it rose so that at the end of two hours it was higher than at the beginning of the test period. Of the substances used, the calcium carbonate, the alumi-



Curves showing peptic activity and pH following test meal plus 6 gr. of a magnesium hydroxide mixture taken immediately after ingestion of test meal and one hour later.

for the longest time (i.e. forty-five to sixty minutes) even though at the end of the two-hour period the

TABLE I
Average pH and Peptic Activity as Obtained in 24 Peptic Ulcer Patients Following (a) Ewald Meal and (b) Ewald Meal Plus Calcium Carbonate, Aluminum Hydroxide, Magnesium Hydroxide, or Sodium Lauryl Sulfate (Aspirations at 15 Minute Intervals).

		ASPIRATIONS								
	Fasting Stomach		15 Minutes	30 Minutes	45 Minutes	1 Hour	75 Minutes	90 Minutes	105 Minutes	2 Hours
pH	2.8	Ewald Test Meal	2.6	1.8	1.6	1.5	1.9	1.6	1.7	1.5
Peptic* Activity	1,620		1,150	1,230	1,400	1,570	1,500	1,640	1,670	1,760
pH	2.9	Ewald plus Calcium Carbonate (2 Gm.)	5.4	4.0	2.6	2.2	1.8	1.7	1.7	1.7
Peptic Activity	1,450		710	960	1,320	1,450	1,570	1,810	1,770	1,720
pH	3.2	Ewald plus Aluminum Hydroxide (8 cc.)	5.1	3.7	2.3	2.5	2.1	1.7	1.7	1.8
Peptic Activity	1,400		650	860	1,280	1,230	1,550	1,720	1,760	1,710
pH	2.6	Ewald plus Sodium Lauryl Sulfate (100 mg.)	2.7	2.1	2.1	2.0	1.9	2.0	1.9	1.7
Peptic Activity	1,310		1,040	1,130	1,320	1,520	1,620	1,640	1,750	2,000
pH	2.8	Ewald plus Sodium Lauryl Sulfate (200 mg.)	3.1	2.2	1.7	1.7	1.8	1.7	1.6	1.5
Peptic Activity	1,310		970	1,200	1,400	1,570	1,560	1,650	1,800	1,750
pH	3.5	Ewald plus Magnesium Hydroxide Mixture (6 gr.)	4.6	3.0	2.1	1.4	1.3	1.4	1.4	1.4
Peptic Activity	1,310		591	990	1,270	1,440	1,600	1,671	1,743	1,713

* Peptic activity measured in milli-units.

TABLE II
Average pH and Peptic Activity as Obtained in 12 Peptic Ulcer Patients Following Ewald Test Meal and After Ewald Test Meal Plus Sodium Lauryl Sulfate and Magnesium Hydroxide at Hourly Intervals (Aspirations at Half Hour Intervals).

	Fasting Stomach		1/2 Hour	1 Hour	1 1/2 Hours	2 Hours
pH	3.7	Ewald Test Meal	3.0	1.7	2.0	1.7
Peptic Activity*	1,250		980	1,010	1,390	1,460
pH	3.6	Ewald plus Sodium Lauryl Sulfate (100 mg.)	2.9	1.7	1.3	1.3
Peptic Activity	1,210		800	1,200	1,340	1,520
pH	3.0	Ewald plus Sodium Lauryl Sulfate (100 mg.) (Duplicate Test)	3.6	2.0	1.6	1.5
Peptic Activity	1,070		930	1,290	1,290	1,430
pH	3.7	Ewald plus Sodium Lauryl Sulfate (200 mg.)	4.2	3.6	3.1	1.9
Peptic Activity	1,040		630	1,190	1,050	1,500
pH	3.6	Ewald plus Sodium Lauryl Sulfate (200 mg.) (Duplicate Test)	2.0	1.9	1.7	1.6
Peptic Activity	1,480		810	1,270	1,470	2,070
pH	3.9	Ewald plus Magnesium Hydroxide (6 gr.)	2.4	2.0	2.4	1.9
Peptic Activity	1,150		1,100	1,350	1,650	1,500

values of either were not much different from those obtained with the test meal. In our study we did not observe any marked difference in the antipeptic effect between aluminum hydroxide and calcium carbonate as described by some (13, 14, 15). This, however, might be explained by the fact that we did not use amphojel as the others did.

Interestingly, neither the pH nor the pepsin output was in any way affected by the administration of 100 mgm. of sodium lauryl sulfate; the pepsin activity, if anything, being highest on this test day. Only after the administration of 200 mgm. of sodium lauryl sulfate after the test meal was there a slight rise in the pH and a decrease in the peptic activity noted. It is also important to note that the administration of a second dose (100 or 200 mgm.) of sodium lauryl sulfate after one hour did not in any way influence the pH or peptic activity, i.e., the pH continued to drop and the peptic activity in these patients was not any different from that of the patients receiving the test substance only once (shortly after the test meal). It was also interesting to note that following the administration of a second dose (6 gr.) of magnesium hydroxide, there was a slight rise in the pH but the peptic activity was not in any way affected.

In all cases the peptic activity seemed to be associated with alteration of the pH. Decreased peptic activity was usually associated with increase in the pH. The influence on the peptic activity by the various substances tested was proportional to their raise of the pH. Sodium lauryl sulfate, too, seemed to decrease the peptic activity while raising the pH. A similar failure of sodium lauryl sulfate to cause inhibition of peptic activity in peptic ulcer patients on the usual milk and cream hourly feeding was reported by Kirsner and Wolff. (16) The latter, however, noted inhibition of peptic activity if the diet was free of phospholipids.

Realizing that the number of patients tested clinic-

ally with sodium lauryl sulfate was rather small and that the time they were under observation was comparatively short, it may nevertheless be stated that the clinical course of these patients was not strikingly different from that of the patients taking other types of ulcer medication. The fact that the sodium lauryl sulfate had to be taken at hourly intervals inconvenienced quite a number of these patients and for this reason attempts were made to decrease the medication to every two hours. These attempts had to be abandoned when the symptoms became aggravated. In two patients, whom we were able to follow up for the longest period, reoccurrence of symptoms occurred shortly after the sodium lauryl sulfate was stopped indicating that apparently no cure had resulted. A third patient—observed for fifteen months—had as many recurrences of his ulcer symptoms while taking sodium lauryl sulfate irregularly as while taking any other medication. As a whole, the group of sodium lauryl sulfate (especially when they became ambulatory patients and left the hospital) were uncooperative because of the necessity for frequent medication which might explain the difficulty of accumulating a larger series of cases.

SUMMARY AND CONCLUSION

1. Calcium carbonate and aluminum hydroxide preparation, magnesium hydroxide and sodium lauryl sulfate caused decreased peptic activity simultaneously with a rise in the pH.

2. Calcium carbonate, the aluminum hydroxide preparation and magnesium hydroxide caused more marked peptic inhibition than sodium lauryl sulfate.

3. In our studies we were unable to confirm the reported observations that sodium lauryl sulfate inhibits peptic activity in the presence of an unaltered pH.

4. Clinical use of sodium lauryl sulfate on a small number of patients on the usual dietary peptic ulcer management failed to reveal any superiority of this medication over some of the other medications used.

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ADDENDUM

Since this paper was submitted a report (Kirsner, J. B. & Wolff, R. A., *Gastroent.* 2:93, 1943) appeared in which the healing of gastric ulcers was not affected by very large quantities of sodium alkyl sulfate and a low fat diet.

Vitamins and Hormones In Nutrition

By

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ALTHOUGH our knowledge of vitamins has increased tremendously in the last ten years, the present status of vitamin therapy still leaves much to be desired. The importance of vitamins in the diet has been so loudly acclaimed in the popular and scientific press that it has led to their indiscriminate use, both by laymen and by many physicians. The literature on vitamins, both scientific and popular, is so massive that its magnitude, in itself, aside from its many contradictions, indicates our lack of understanding of these vital food accessories. Similarly, enormous progress has been made in the recognition of hormones and their chemistry. Here too, copious volumes have been written in the scientific and popular press, discussing their individual physiological action, and their interrelationship. Unfortunately, however, little attention appears to have been given to the relationship between vitamins and hormones, in their clinical application. The responsibility for many therapeutic failures has frequently been attributed to the vitamin, when actually the underlying cause has been the inability of the organism to utilize the vitamin because of unrecognized or untreated endocrine dyscrasias. The purpose of the present communication is to discuss and to present evidence of the synergistic action of vitamins and hormones in their relation to nutritional deficiencies.

Considerable data have been presented in the literature (1-4) to indicate that pathology of the gastrointestinal tract interferes with vitamin absorption. More recently it has been shown that certain bacteria synthesize vitamins (5-7) while others may destroy them or inhibit their synthesis (8-9) by destruction or interference. Furthermore, numerous investigators (10-11) have demonstrated that hormones are essential to normal nutrition and good health. The role of the anterior pituitary gland (12) and the pancreas (13) in carbohydrate metabolism has long been known, and more recently the adrenal (14) and sex glands (15), as well as the endocrines as a whole (16), have been found to affect carbohydrate metabolism. Protein metabolism (17) may also be directly influenced by the glands of internal secretion. Likewise, the effect of hormones on fat metabolism (18) has been described. Experimental research on animals has proven that endocrine dyscrasias will bring about nutritional abnormalities (19, 20). Clinically, in humans, endocrine dyscrasias can bring about nutritional disturbances, and present such bizarre and opposite pictures as the cachexia of Simmond's disease and the disproportionate obesity of acromegaly and myxedema. Conversely, vitamin imbalances have produced hypo- and hyper-

activity of the endocrine glands (21, 22). Thus the similarity between vitamins and hormones in their influence on nutrition is evident.

In view of these findings, is it not conceivable that one group affects the other, or that the two function synergistically? Volumes of scientific literature have been published, much propaganda has been promulgated in lectures, radio programs, and advertisements on vitamin requirements, particularly in reference to the factors of the vitamin B complex, but apparently little or no attention has been paid to the ability of the organism to utilize these vitamins. Any attempt to supply the daily requirements, whether from foods or from synthetic preparations, is useless if primarily the organism is unable to metabolize the vitamin. For instance, infection anywhere in the body may inhibit the final synthesis of vitamins. Also, faulty intake over a long period of time, or marked emotional upset, may be inhibiting factors (23). Endocrine deficiencies, such as are commonly seen at the climacteric period (24), may interfere with synthesis of vitamins. On the other hand, as a result of the inability of the organism to properly absorb sufficient vitamins, secondary hormone dyscrasias may develop. In short, the organism must be in normal biological and physiological balance before vitamins can be properly utilized (25-26).

The influence of the climacteric period on vitamin absorption, as seen in the following case, is frequently encountered. A woman, aged 46, complained of fatigue, emotional instability, irritability, and gain in weight of two years' duration. Her health had always been good until the onset of the present symptoms. Previous attempts at vitamin therapy had been ineffective. Physical examination and laboratory data were negative except for definite evidence of endocrine deficiency and avitaminosis. At this time the patient could have been given pounds of B complex, but it would have been wasted medication. However, treatment consisted of readjustment of the endocrine balance by substitution therapy, and administration of vitamins. Within a few weeks the patient was free from complaints, and clinically greatly improved. In this case the synergistic action of hormones on vitamin metabolism was apparent. In his work on achromotrichia (27-28) the author has tried to point out this synergy.

The effect of infection and glandular deficiency on vitamin absorption is illustrated by the case of a man, aged 32, who complained of sluggishness, depression, frequent colds, and beginning achromotrichia, of several years' duration. Vitamins self-administered during this period had failed to relieve the symptoms. At examination badly diseased tonsils were found, and

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definite evidence of hypothyroidism and avitaminosis. The tonsils were removed and the endocrine balance adjusted by the oral administration of thyroid hormone. Vitamins were given orally. Within a few weeks complete disappearance of the general symptoms was observed. This case emphasizes how the two factors, metabolic disturbance and infection, can interfere with vitamin absorption. Correction of a single factor in this picture would have been ineffective, but with the removal of the tonsils, and the administration of thyroid, the vitamin was properly synthesized. The previous therapeutic failure had been falsely attributed to vitamin ineffectiveness.

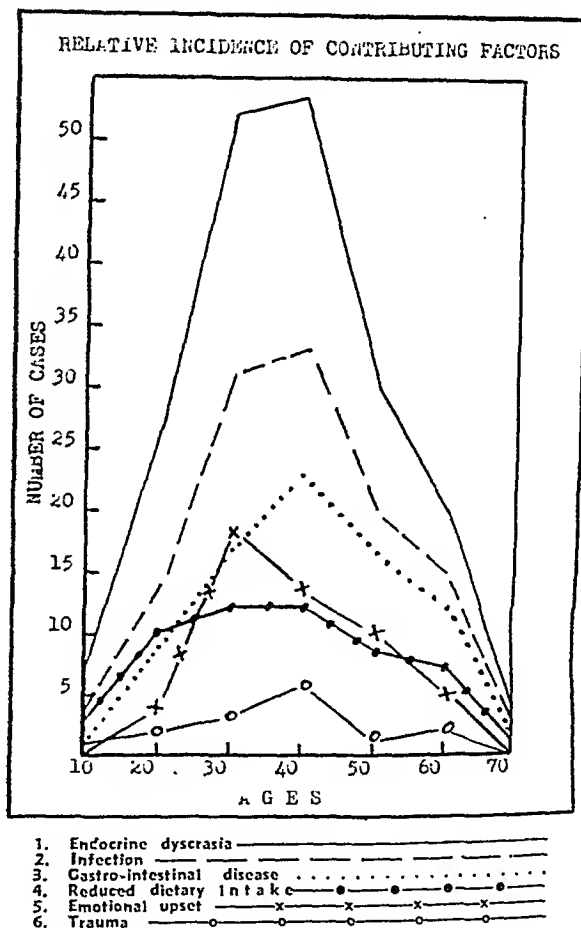
The influence of infection at the male climacteric age on the nutritional state, is strikingly illustrated by the following case with chronic non-purulent drainage. A 52 year old male had suffered from acute empyema about thirty years prior to the present examination, resulting in continual serous discharge from a sinus following thorocoplasty of the right chest. Physical examination revealed obesity, hypertension, acne, prostatic infection, avitaminosis, and thyro-androgen deficiency, as well as the chronic empyema sinus. A course of prostatic massages was instituted to eradicate the focus of infection. Hormones were given parenterally to restore the endocrine balance, and a potent elixir of the vitamin B complex was administered orally, in combination with massive doses of vitamin A. With the clearing of the prostatic infection, and restoration to a normal endocrine balance, the clinical signs of avitaminosis diminished, and improvement was observed in the discharging sinus. During the past four months, that is, after nine months of therapy, the patient has been free from chest sinus drainage for the first time in fifteen years, his acne is completely cleared, and the blood pressure is somewhat reduced.

Gastro-intestinal disease of functional origin is frequently a precipitant factor in producing hormone and vitamin deficiencies. A male of 35 complained of nervous irritability, insomnia, fatigue, achromotrichia and so-called colitis persisting for five years. Vitamins administered orally during this period were ineffective. The diagnostic problem resolved itself into discovering a possible focus of infection, or endocrine imbalance, a true pathological condition in the gastro-intestinal tract having been ruled out first. At examination definite signs of endocrine imbalance and avitaminosis were noted. Laboratory data corroborated this diagnosis. A bland diet, fortified with banana powder, was used to decrease the irritation on the mucosa of the gastro-intestinal tract, as well as the irritation from food bulk. This palliative treatment had been used previously with no improvement in symptoms, but when endocrine therapy was instituted, and vitamins were given orally and parenterally, the bowel condition began to clear. No further treatment was given for the so-called colitis itself. The results that followed were due to the restored balance of the hormone system, and beginning improvement in synthesis and absorption of vitamins, which further produced normal enzymic se-

cretion, leading to normal peristalsis and resulting in physiological bowel action.

In a series of 200 cases the author has encountered these concurrent findings, endocrine dyscrasias and vitamin deficiencies. The incidence of other contributing factors, such as infection, trauma, gastro-intestinal disease, reduced dietary intake, and severe emotional upset, may vary, but hormone and vitamin imbalance have been almost constant. Chart I presents graphically the relative incidence of these contributing factors, analyzed according to age. Endocrine dys-

CHART I



crasias occurred in 193 cases, 96.5%. Infection was of next highest incidence, 120 cases, 60%. Gastro-intestinal disease was found in 81 cases, 40.5%; reduced dietary intake in 53 cases, 26.5%; emotional upset in 50 cases, 25%; trauma in 15 cases, 8%. It is evident from analysis of these figures, and the chart, that one or several of these factors may occur in any individual case, in addition to the hormonal imbalance. Administered orally, vitamins by themselves were ineffective in the majority of cases in this series. Vitamin therapy was successful only after the underlying conditions had been cleared up, and hormone balance established by substitution therapy.

It has been the author's practice to obtain on all patients an accurate history, and complete physical examination, including routine urine, blood counts and

smears, fasting blood sugar, nonprotein nitrogen, and and basal metabolic rates. Careful examination was made for all foci of infection, particularly prostatic involvement in male patients. Treatment consisted of eradicating all foci of infection, adjusting the endocrine balance by substitution therapy, prescribing a well proportioned diet, and administering vitamins orally and parenterally.

The author recognizes that such an elaborate regimen may not be practicable in all cases for diverse reasons. However, extensive laboratory studies, as desirable as they are, may not always be necessary if more attention is paid to apparently trivial complaints and minute physical changes. Brittle nails, gray hair, pigmentation, fatigue, all insignificant in themselves, become important when subnormal temperature, slow pulse, dry skin, atrophic papillae of the tongue, and low blood pressure are encountered at physical examination, for the clinical picture thus obtained indicates a true deficiency state. Careful examination, detailed history, and proper evaluation of the most insignificant symptoms, will often reveal the type of deficiency, and the underlying endocrine dyscrasia. Only by eradicating the cause of the deficiency and restoring the endocrine balance, can vitamin therapy be successful.

Science has advanced by a succession of trials and errors, failures and successes, which have led, by paths that were at times barely discernible, to facts that today are obvious; to doubts today that yesterday were dogmas; to hypotheses that perhaps tomorrow will be truths. Such, it is hoped, will be the case of the hypothesis presented above, that physiological substitution therapy may one day be accepted and incorporated into the routine practice of medicine.

SUMMARY

1. The synergistic action of vitamins and hormones has been indicated.
2. The influence on vitamin absorption of such contributing factors as hormone dyscrasias, infection, gastro-intestinal disease, reduced dietary intake, emotional upset, trauma, has been discussed.
3. Careful examination, complete history, proper evaluation of apparently insignificant symptoms, with routine laboratory tests whenever practicable, are essential for correct diagnosis.
4. Therapeutic recommendations consist of clearing all foci of infection and contributing factors, restoring the endocrine balance by substitution therapy, and administration of vitamins.

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Changes In Sensitivity To Allergenic Foods In Arthritis

By

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THE relation of nutrition and arthritis demands consideration in view of the findings in this stubborn troublesome widespread disease. "The newer knowledge of nutrition is the greatest advance," says McCarrison, "since the days of Lister; . . . it will do for medicine what asepsis has done for surgery."¹ This broad claim has to be sustained by much investigation, which no doubt will disclose much concerning the anemias, tuberculosis and cancer, osteomalacia, skin diseases, nerve disorders, and the like. The writer narrows his investigation to one particular, namely, the relation of allergy to arthritis.

Describing work with arthritis by means of diets to which these patients are allergic, the writer in 1924 published these articles: "*The Relation of Anaphylactic Disturbance to Arthritis*,"² and "*Food Allergens in Connection with Arthritis*."³ These articles show definitely the advantage of the cutaneous test in arranging a diet for arthritic patients. In work subsequently done the author is still enthusiastic and convinced that allergy is an important factor in arthritis, and that the results are very satisfying both to patients and physicians. It has been his privilege during this time to follow up many of the cases previously tested by the cutaneous method, with diets arranged accordingly, and to observe the wonderful results obtained by this method. Many interesting developments have been noted during this further interval of nineteen years. Indeed his percentage of complete relief from all arthritic disturbances has greatly increased.

It is difficult to evaluate the etiology of an allergic disease because of the multiple food sensitizations. Skin reactions seem to have less bearing on constitutional sensitizations than in the case of the inhalants. Nevertheless diagnostic aid is obtained from elimination diets as well as the blood response. It is impossible to avoid the conclusion that food is a factor in arthritis, in addition to many other diseases. A composite clinical picture of allergy due to ingesta is presented in the case of arthritis studied here. One has to be familiar with the factors modifying the allergenic effect of food, and also with the symptomatology. Hypersensitivity to food is to be suspected in many arthritic cases, though the immunological nature of this allergy may be quite complex, such as the quantitative and the cumulative factors. Likewise the condition of the food itself, whether cooked or raw, has something to do with the allergic response. Furthermore, not all genetically related foods become etiologic.¹

An important point to be observed is that there is

change in sensitivity to foods which develops in arthritic cases. The reduction of allergic diets is a method which accomplishes excellent results and gives relief to many patients by this means kept in an excellent condition. Those cases who consulted the writer years ago and had a diet worked out by the cutaneous method, the foods to which they were sensitive then being eliminated from the diet,—these patients were relieved of their arthritic disturbances and indeed would continue free from arthritis. When, however, they ate some of the banned foods, their symptoms would reappear. Patients adhering strictly to the diet as outlined became free from arthritic attacks until such time as changes took place in their systems, and their sensitivity to foods would be changed.

Arthritis is not a problem that is by any means more or less hopeless. Says a practitioner in a large public hospital, "On the basis of allergy, is it not possible that there may be some factor common to all streptococci that is capable of producing arthritis? It may be a protein or a toxin, cause of arthritis can be found only if we work on the allergic theory."²

Though the bulk of investigations in the field of arthritis and allergy has been worked out abroad, there is evidence of the gradual acceptance of the relation that is traced in this article. "Diet as an etiologic factor," says Wyatt, "is important not only in quality but in quantity. The metabolic and mechanical loads should be reduced. A lack of vitamin, as F and G, should be restored in adequate amounts."³

As an illustration of the point, if chicken was one of the foods which the patient could safely eat, then after a lapse of time, the certain changes in the individual's system might be such that the eating of chicken would actually provoke arthritic disturbances. Furthermore, and conversely, foods that once were contra indicated, which for example may be beef, this being taken into the system for a considerable length of time might ultimately turn out to be a food to which the patient is not allergic. This change of susceptibility does not always occur with all foods which are either good or bad for the individual. There are some foods to which these patients may always remain sensitive, and may never eat without causing arthritic disturbances, while others may change at intervals. The time of these changes in sensitivity to the foods occasioned in arthritic cases seems to vary with each individual. This change in sensitivity may be influenced distinctly by the frequent eating of the food to which a patient at the time of testing is non-allergic who becomes susceptible later by such frequent eating of considerable quantities as to occasion a breaking down within his system of the im-

¹ Submitted Dec 10, 1943.

² McCarrison, *British Medical Journal*, 2, 6111 (Sept. 25) 1936.

³ Turnbull, *Hourn, Am. M.A.* (May 31) 1924, 82:1757-1759

⁴ Turnbull, *Boston Med. and Surg. J.*, 191, No. 10. (Sept. 4) 1924, pp. 438-440.

⁵ Vaughan, Warren T.: *Food Allergens, I A Genetic Classification with Results of Group Testing.* *J. Allergy*, 1:385, 1930

⁶ A. Cohen, *Jefferson Medical College Hospital, Philadelphia, Internat. Clin. Vol. III, 47th series, Sept. 1937, p. 288.*

⁷ B. L. Wyatt, *Medical Journal and Rec.*, 133: 369. (Apr. 13) 1931

munity to that particular food. On the contrary if an individual, allergic at the time of testing to particular food, abstains completely from this food, the individual cells within the system can in time in many instances develop immunity to this allergenic food. Other conditions can also contribute to these changes in the sensitivity of patients to food, namely, infections, serious illness, especially if of long duration, lowering the resistance of the individual.

The time of these changes in sensitivity may vary somewhat in different individuals. But it is the writer's experience that with very few exceptions these fluctuations in sensitivity are not sufficient to produce any disturbance in these arthritic patients for at least one year following the time of testing. Some individuals will go one and one half years before any manifestations of allergic arthritis. Occasionally, some may go two years or longer and certain cases have gone ten years without any arthritis, on the original diet as arranged by the cutaneous tests. In order to keep these patients in the best possible condition, free from arthritic disturbances and without taking chances, it is advisable that they be tested in one year following the previous test and then followed up each succeeding year. A number of arthritic patients make appointments for these tests and examinations each year, which shows the faith that these patients have in the diets arranged by this method and the excellent results obtained.

To confirm the statements made in this paper, some cases are herewith cited, so as to illustrate these changes.

Case 1.

Female, aged 50. In consultation July 28, 1920. Arthritis ten years, affecting all the phalangeal articulations of both hands with such enlargement of the joint structures that there was a space of at least one quarter inch between all contiguous fingers. This enlargement was greatest at the middle between all contiguous fingers. This enlargement was greatest at the middle phalangeal articulations. The joints of both hands were very sensitive, with much swelling of the para-articular tissues and redness of the cutaneous surface. Both shoulders were extremely sensitive; marked tenderness, very painful, and at the least motion caused much distress. A diet was worked out for this patient by the cutaneous method; patient instructed to follow this diet strictly. At this time the patient showed a cutaneous reaction to rice, chicken, beef, haddock, which foods were banned. In ten days there was less tenderness and swelling in the joints. In four weeks all the para-articular swelling and tenderness had completely disappeared. There was continuous diminution of the phalangeal bone structure so that in ten months the joints were normal and fingers could be approximated. This patient continued on this diet until I was consulted again on June 3, 1924. The history at this time was no disturbance until April 20, 1924, when fingers began to become tender and swollen, and this continued to increase. Tests were again made to arrange a diet to conform. Rice, beef, and haddock were ascertained to be foods which the patient could now eat, while chicken still remained an irritant. Corn and lamb which

did not give reactions on the 1920 diet were found in this test to be bad for the patient. Following the corrected diet, the patient was entirely relieved of all arthritic disturbances in four weeks, and continued free until August 1, 1926, when she commenced to have stiffness, pains in the fingers, shoulders and knees. A diet was worked out on August 18, eliminating wheat, chicken, lobster, spinach, grapes. After following the new diet for two weeks, patient was relieved of all pains and continued free of pain until April 1, 1930. I was again consulted by this patient on May 21, 1930. Cutaneous tests were made and reactions were obtained to oatmeal, milk, cheese, peas, tomato, orange and spinach. Following this diet the patient was free from all pain and arthritic disturbance in four weeks. December 1, 1932, this patient had no symptoms but requested that a diet be worked out in order to prevent disturbances and keep in best possible condition. Cutaneous tests made and reactions were obtained from oatmeal, beef, eggs, white potato, coffee, apple. This patient continued well until April 15, 1934 when she began to have some stiffness in the cervical region. She consulted me May 14, 1934 and a diet worked out by the cutaneous method showed reactions to corn, lamb, beef, spinach, melon, and pineapple. This stiffness in the cervical region was relieved in three weeks' time and she continued free from pain but returned in August 1936 for test and examination. No arthritic symptoms. Testing at this time showed reactions to corn, lamb, pork, lobster, spinach and grapes.

In looking back over the tests during these periods we find in 1920 the patient gave reactions to rice, beef and haddock; in 1924 these foods gave reactions, while in 1924 corn and lamb were bad for this patient. In 1926 wheat, chicken, lobster, spinach and grapes were bad but corn proved an irritant which in 1924 gave no reaction. Chicken showed bad for this patient for six years. In 1930 reactions were obtained to oatmeal, milk, cheese, peas, tomato, orange, and spinach. Lobster which was bad in 1926 was approved for the patient. December 1932 we find that oatmeal and spinach which obtained reactions in 1930 and 1932 still show reactions. While beef was right for the patient to eat in 1930, in 1932 it gave a reaction. In 1934 beef still proved reactive. In 1932 oatmeal and apple and coffee which gave reactions do not show in 1934. In 1934 and 1936 lamb gave reactions, while spinach was consistently shown as bad for the patient in every test from 1926 to the present time.

Case 2.

Female, age 57. Consulted me June 2, 1924 for arthritis affecting the hands, shoulders, hips, knees, and feet. There was much tender swelling of affected joints, with great stiffness and distress in motion. This complication had been steadily growing worse for ten years. Tests were made and reactions obtained for oatmeal, chicken, eggs, cheese, halibut, olives, and raspberry. The patient was put on a diet and in two weeks showed distinct improvement; in four weeks could move about without distress, and in three months was free of all arthritic disturbances. This patient again returned in September 20, 1926, the past four weeks hav-

rapidly worse and painful. This patient was tested and gave reaction to pork, egg white, flounder, peas, onion, molasses, orange, apricot, and chicken. The patient was put on a diet omitting these foods and in fifteen days, arthritis showed 50 per cent reduction. In four weeks the improvement was 80 per cent, and in six weeks she was completely relieved of all pain. On October 15, 1936, patient complained of pains in the fingers which were very stiff, and also much soreness in both shoulders and knees. These symptoms started three months previously. Tests were made and reactions obtained to beef, milk, egg yolk, clams, beets, broccoli, orange, and plums. After patient avoided these foods, in two weeks showed 50 per cent improvement, in four weeks 80 per cent, and in seven weeks completely relieved of all arthritic disturbances. This patient was sensitive to egg white in 1934 but could tolerate it in 1936. In neither 1934 nor 36 could she eat egg yolk. Oranges were bad for this patient in both 1934 and 1936. Plums she could eat in 1934 but in 1936 they could not be tolerated.

Case 6.

Female age 51. Consulted by this patient on August 18, 1925. Pain in the hands for four years much worse the last four months. Pain in the lumbar vertebrae. Much pain and soreness and stiffness in both sacro-iliac articulations. Cutaneous tests proved reactions to wheat, veal, cheese, shrimp, turnip, tomato, tea, egg white, and rhubarb. By avoiding the foods to which the patient was sensitive, by September 29, she was free from all pains.

Again consulted by this patient on March 28, 1928. She was sensitive to lamb, egg yolk, haddock, potato, endive, coffee, and orange, and was put on a diet other than those foods. By April 20, the patient was completely relieved of all pains. This patient who could eat lamb in 1925 diet, had to avoid it in the 1928 diet. Egg white which was bad for the patient in 1925 was well borne in 1928.

This patient was not seen again until March 4, 1935 and at this time was having severe pains in the lumbar articulations, both sacro-iliacs, both shoulders and knees. Tests were made and reactions found to rice, beef, turkey, lobster, sweet potato, escarol, orange, blackberry. Patient was put on a diet excluding these items and March 19 was greatly relieved of all pains, except for occasional pain in the sacro-iliac. On April 1, there was complete relief of all arthritic disturbances. In 1928 it is noteworthy that the patient could eat beef, rice, and blackberry, while in 1935 the tests showed them to be allergens. This patient next consulted me in October 1936. Though free from any arthritic disturbances, she was going to Florida to spend the winter and wishing to keep well, thought it advisable she should have the tests again made since 19 months had elapsed. It was advisable to take all precautions. The test gave reactions to pork, egg, scallop, cabbage, olives, fig, grapes. Here on the 1935 diet the patient could not have sweet potato or escarol which were allowed on the 1936 diet. In this case orange is found contrary in 1928-1935-1936 tests. This patient is now free from all arthritic disturbances.

Case 7.

Female, age 53, consulted April 14, 1930 for arthritis which started in July 1928. Came on very suddenly. She went to bed and woke up in the morning with a very stiff neck. Arthritis also present in both wrists, ankles, and sacro-iliac, both hands and knees. The arthritis gradually becoming worse, involving the cervical vertebrae so that the patient was unable to rotate to the right over five degrees and to the left 10 degrees. Fixation of the cervical vertebrae was such that the patient was unable to move the head forward or backward. Tests were made and reactions obtained for corn, chicken, halibut, oyster, kidney beans, asparagus, swiss chard, chocolate and walnut. A diet was arranged so that the patient avoided these foods. By May 2, 1930 there were no pains in the hands, feet, knees, while the pains in the neck, sacro-iliac, and ankles were relieved 50 per cent. The rotation of the head to the right 10 degrees and to the left 20 degrees. By May 19, she was completely relieved of all pains. There was greater motion of the head to both the right and left and up and down. By June 10, the patient was free of all pain and the motion of the head in all directions was normal. This patient returned February 8, 1933 with pains in the knees, sacro-iliac, some stiffness in the cervical vertebrae. A diet was again arranged by the cutaneous tests and the patient was found to be sensitive to corn, chicken, egg white, shad, oyster, lettuce, apple, and apricot. On avoiding these foods, by February 28, the patient was relieved 60 per cent of all her arthritic disturbances. March 10, was 85 per cent relieved of all arthritic tendencies, and March 28, complete relief. Here in 1930 and 1933 we find that the patient gave reaction to both pork and chicken. In 1930 the patient could eat egg but in 1933 the egg white was bad and the patient could tolerate egg yolk. On the 1930 diet the patient could safely eat lettuce and apricots, but in the 1933 diet she had to avoid these. Kidney beans which were bad in the 1930 diet were allowed in 1933. October 15, 1935, I was again consulted by this patient. She had been free from all arthritic disturbances until September 1, 1935, when she began to have pains in the fingers, hands, knees, and both cervicle articulations. She was found sensitive to oatmeal, soy-bean flour, egg yolk, crab, cauliflower, grapefruit, honey dew melon, and apricots. After the patient avoided these foods, by November 1, 1935 there was 60 per cent less pain in the articulations. On November 23, there was complete relief of all arthritic pain. Chicken which had been proscribed in both 1930 and 1933 diet lists, the patient could eat in 1935. The egg yolk which was well borne in the 1933 diet, was bad on the 1935 diet. Apple which was bad in the 1933 diet, was included in the 1935 diet. Grapefruit which was good on the 1933 diet turned contrarywise on the 1935 diet. Though two years have elapsed since the last test was made on this patient, she telephoned the week of Oct. 1, 1937 that she was feeling fine and free from all arthritic pains.

Case 8.

Male, age 71. Consulted me November 14, 1932 for arthritis which began in 1922 in the index fingers af-

then consulted me and was immediately instructed to follow strictly the diet as prescribed by the tests of August 18, 1931. In two weeks there was 70 per cent relief, and in four weeks complete relief was noted from all arthritic disturbances. Bad at tests made in 1926 and 1931, was oatmeal: bad at the first test but not at the second was chicken, salmon, and corn. Bad the first test was yellow eye beans but good at the second test with the kidney beans.

Was again consulted December 4, 1935. Pain, stiffness in both knees for four weeks. Tests made showing reactions to rice, lamb, lobster, pea beans, carrots, and pears. By eliminating foods to which allergic was 70 per cent relieved in two weeks, and completely so in four weeks. In this test, oatmeal which was bad the previous two tests, was non-allergic. In the third test rice and rye which were bad, proved well borne by the first and second tests. Chicken was bad in the first test but not in the second and third tests. Orange, unfavorable in the second test, was good for the patient in the first and third tests. Yellow eye beans bad in the first test but good in the second and third tests while kidney beans bad in the second test proved good in the first and third tests. Pea beans were bad in the third test but otherwise in the second and third tests. Thus showing that one of these beans gave reaction to each one of these tests and in making tests it would not be

wise to use any one of these beans as representative of the legumes.

TESTS MADE BUT NO SYMPTOMS OF ARTHRITIS

Case 1. Fifth test in which there had been an interval of two years and seven months since the fourth test.

Case 2. Tests made twice in which there were no symptoms each two years following the last test, these being the fourth and fifth tests.

Case 6. Third test, no arthritis after an interval of one year seven months since the second test.

Case 7. Two years since the last test made October 15, 1935, this being the third test.

Case 8. No symptoms of arthritis, third, fourth, and fifth tests. November 1, 1935 traumatism to shoulder and hip. Tests were made December 10, 1935 on account of traumatism. This patient is tested each year in order to keep in good condition.

Although tests were made on these patients with no arthritic symptoms there were changes in their sensitivity to foods. Although there were changes in sensitivity, the accumulation of these foods to which they were allergic in the system had not reached the stage sufficient to cause arthritic disturbances, but if these patients had continued over a longer period then the accumulation in the system of these allergens could cause arthritic disturbances.

TABLE I.

Case	S	Age	DC	Dur	RS	NDRS	IT	NT	NDRF	TCR	TFS
1	F	50	July 28, 1920 June 3, 1924 Aug. 18, 1926 May 21, 1930 Dec. 1, 1932 May 14, 1934 Aug. 1, 1936	10 yrs.	Apr. 20, '24 Aug. 1, '26 Apr. 1, '30 No arthritis Apr. 15, '34 No arthritis	44 dys. 18 dys. 50 dys. none 30 dys. none	4 yrs. -- 26 mos. 4 yrs. 2 yrs. 7 mos. 1 yr. 5 mos. 2 yrs. 3 mos.	1st 2nd 3rd 4th 5th 6th 7th	10 dys. 4 wks. 2 wks. 2 wks. No arth. 3 wks. No arth.	4 wks. 2 wks. 2 wks. No arth. 3 wks. No arth.	3 yrs. 8 mos. 2 yrs. 2 mos. 3 yrs. 9 mos. No arth. this test 3 yrs. 11 mos. 2 yrs. 3 mos.
2	F	57	June 2, 1924 Sept. 20, 1926 Mar. 6, 1928 Mar. 3, 1931 Mar. 30, 1933 Apr. 14, 1935 June 14, 1937	10 yrs.	Aug. 21, '26 Feb. 22, '28 Feb. 5, '31 No arthritis Apr. 1, '35 No arthritis	30 dys. 14 dys. 28 dys. none 14 dys. none	2 yrs. 3 mos. 1 yr. 6 mos. 3 yrs. 2 yrs. 2 yrs. 1 mo. 2 yrs. 2 mos.	1st 2nd 3rd 4th 5th 6th 7th	2 wks. 10 dys. 4 wks. 3 wks. 3 wks. 3 wks. 3 wks.	3 mos. 3 wks. 4 wks. 3 wks. 3 wks. 3 wks. 3 wks.	2 yrs. 2 mos. 2 yrs. 4 mos. 2 yrs. 8 mos. 4 yrs. 2 yrs. 2 mos.
3	F	50	June 23, 1921 Mar. 1, 1930 July 18, 1932 July 10, 1934 June 22, 1937	10 yrs.	Jan. 1, '30 May 1, '32 June 1, '34 Mar. 1, '37	60 dys. 48 dys. 40 dys. 73 dys.	8 yrs. 8 mos. 2 yrs. 3 mos. 2 yrs. 3 yrs.	1st 2nd 3rd 4th 5th	1 mos. 2 wks. 15 dys. 10 dys. 4 wks.	2 mos. 5 wks. 1 mo. 5 wks. 2 mos.	8 yrs. 4 mos. 2 yrs. 2 mos. 2 yrs. 2 yrs. 5 mos.
4	F	54	Apr. 6, 1927 Aug. 10, 1931 Dec. 4, 1935	5 yrs.	May 12, '31 Nov. 5, '35	91 dys. 32 dys.	4 yrs. 4 mos. 4 yrs. 4 mos.	1st 2nd 3rd	2 wks. 10 dys. 2 wks.	6 wks. 6 wks. 7 wks.	4 yrs. 4 yrs. 6 mos.
5	F	59	July 17, 1934 Oct. 15, 1936	5 mos.	July 15, '36	92 dys.	2 yrs. 6 mos.	1st 2nd	15 dys. 2 wks.	6 wks. 7 wks.	1 yr. 9 mos.
6	F	51	Aug. 18, 1925 Mar. 28, 1928 Mar. 4, 1935 Oct. 16, 1936	4 yrs.	Mar. 1, '28 Dec. 10, '34 No arthritis	4 wks. 90 dys. none	2 yrs. 9 mos. 7 yrs. 1 yr. 7 mos.	1st 2nd 3rd 4th	2 wks. 14 dys. 15 dys. ---	6 wks. 30 dys. 27 dys. ---	2 yrs. 6 mos. 6 yrs.
7	F	53	Apr. 14, 1930 Feb. 8, 1933 Oct. 15, 1935 Sept. 25, 1937	2 yrs.	Dec. 10, '32 Sept. 1, '35 Nearly 2 years since the last test.	60 dys. 45 dys. No arthritis, feels well.	2 yrs. 9 mos. 2 yrs. 8 mos.	1st 2nd 3rd	14 dys. 10 dys. 2 wks.	6 wks. 20 dys. 30 dys.	2 yrs. 6 mos. 2 yrs.
8	M	71	Nov. 14, 1932 Dec. 10, 1933 Jan. 7, 1935 Dec. 10, 1935 Jan. 11, 1937	10 yrs.	Dec. 1, '33 No arthritis Traumatism to shoulder and hip No arthritis	10 dys. none Nov. 1, 1935 none	1 yr. 1 mos. Nov. 1, 1935 1 yr. 1 mo.	1st 2nd 3rd 5th	1 wk. 1 wk. ---	30 dys. 2 wks. ---	11 mos. 1 yr. 1 mo. 1 yr. 1 mo.
9	F	39	July 17, 1934 Oct. 5, 1936	3 mos.	Sept. 7, '36	4 wks.	2 yrs. 3 mos.	1st 2nd	3 wks. 2 wks.	6 wks. 4 wks.	2 yrs.
10	F	52	Feb. 16, 1926 Aug. 18, 1931 Dec. 4, 1935	7 yrs.	July 21, '31 Nov. 4, '35	28 dys. 4 wks.	5 yrs. 5 mos. 4 yrs. 4 mos.	1st 2nd 3rd	2 wks. 15 dys. 2 wks.	4 wks. 4 wks. 4 wks.	5 yrs. 3 mos. 4 yrs. 1 mo.

ABBREVIATIONS

S	Sex	Dur	Duration of arthritis	NT	Number of test
DC	Date of consultation	RS	Return symptoms	NDRF	Number of days relief following test
		NDRS	Number of days return symptoms	TCR	Time complete relief following test
		IT	Interval between tests	TFS	Time free of symptoms

Case 1. Free from symptoms: 2 years 2 months, 3 years 8 months, 3 years 9 months, and 3 years 11 months.

Case 2. Free of symptoms between tests: 1 year 2 months, 2 years 2 months, 2 years 8 months, and 4 years.

Case 3. Shortest period free of symptoms between tests: 2 years 2 months, 2 years 5 months, and 8 years 4 months.

Case 4. Free of symptoms between tests: 4 years, 4 years 6 months.

Case 5. Free of symptoms between tests: 1 year 11 months.

Case 6. Free of symptoms between tests: 2 years 6 months, 5 years 7 months, last test 1 year 7 months no symptoms of arthritis.

Case 7. Free of symptoms between tests: 2 years 6 months, 2 years 7 months, 2 years since last test has no symptoms and feels well.

Case 8. Free of symptoms between tests: 11 months, 2 years 11 months, 11 months. This test made following traumatism of shoulder and hip. 1 year 1 month no symptoms.

Case 9. Free of symptoms: 2 years.

Case 10. Free of symptoms: 4 years 1 month, 5 years 3 months.

TABLE II.
Foods to Which Patients Are Sensitive at the Different Tests

CASE 1									
Test 1	Rice	Chicken	Beef	Lamb	Haddock		Grapes	Milk, Cheese, eggs	
Test 2	Rice Corn	Chicken	Beef		Haddock				
Test 3	Wheat	Chicken			Loft.	Spinach			
Test 4	Oatmeal		Beef			Peas, Tomato			
Test 5	Oatmeal		Beef	Lamb		Potato	Casaba,		
Test 6	Corn						Pineapple		
CASE 2									
Test 1	Oatmeal	Chicken	Beef		Halibut	Olives	Raspberry	Eggs, cheese	
Test 2					Sword Fish	Sweet, carrots		Eggs	
Test 3	Oatmeal				Codfish, oyster	Peas, lettuce			
Test 4			Pork		Haddock	Honeydew	Orange	Egg yolk, milk	
Test 5	Rice		Beef			String beans	Pineapple		
Test 6	Corn		Beef		Mackerel	Tomato	Strawberry, apple	Milk	
CASE 3									
Test 1	Wheat	Chicken	Beef		Salmon, Lobster	Celery, tomato	Grapefruit	Chocolate	
Test 2		Chicken			Codfish, clam	Sweet potato	Grapefruit, apple	Egg	
Test 3		Chicken				Peas, potato	Grapefruit		
Test 4					Crab	Tomato	Blueberry, grapes		
Test 5	Corn		Beef		Salmon, oyster	Lima beans	Lemon, peach, pineapple	Cheese	
CASE 4									
Test 1			Beef	Lamb	Codfish	Peas, Hubbard squash	Tomato, Potato	Coffee, milk	
Test 2			Beef		Scallop	Lettuce	Orange		
Test 3	Rice				Smeit	Onion, parsnip	Banana	Egg white	
CASE 5									
Test 1			Pork		Flounder	Peas, onion	Orange, apricot	Molasses, egg white	
Test 2			Beef		Clams	Beets, broccoli	Orange, plums	Milk, egg yolk	
CASE 6									
Test 1	Wheat		Veal		Shrimp	Turnip, tomato	Rhubarb	Egg white, tea	
Test 2				Lamb	Haddock	Potato, endive	Orange	Cheese	
Test 3	Rice	Turkey	Beef		Lobster	Sweet potato,	Orange, blackberry	Coffee, eggs	
Test 4			Pork		Scallop	Escarol	Figs, grapes		
CASE 7									
Test 1	Corn	Chicken			Halibut	Kidney beans		Chocolate	
Test 2					Oyster	Asparagus		Walnut	
Test 3	Corn	Chicken			Shad, oyster	Swiss chard			
Test 4	Oatmeal				Crab	Lettuce	Apple, apricot	Egg white	
Test 5	Soybean flour					Cauliflower	Grapefruit	Egg yolk	
CASE 8									
Test 1	Rice	Chicken			Salmon, scallop	Potato, tomato	Blueberry		
Test 2	Corn	Turkey	Beef		Halibut, lobster	Summer squash	Cantaloupe, Pineapple	Cheese	
Test 3	Oatmeal		Pork		Codfish, haddock	Watercress	Orange		
Test 4	Rice			Lamb	Clam	Tomato	Banana	Chocolate	
Test 5	Corn		Veal	Pork	Trout	Lima beans	Pineapple		
CASE 9									
Test 1	Oatmeal	Chicken		Lamb	Haddock	Tomato	Grapes		
Test 2	Rye		Beef			Onion, peas	Grapefruit		
Test 3	Oatmeal					Cabbage			
CASE 10									
Test 1	Oatmeal	Chicken	Beef		Salmon	Yellow eye beans	Apple, plums		
Test 2	Corn				Codfish	Kidney beans	Orange, pineapple		
Test 3	White flour			Lamb	Lobster	Pea beans	Pear		
Test 4	Rice					Carrot			
Test 5	Rye								

In these cases, ages at the time of consultation vary from 39 to 71 years of age. One was 39, one 50, one 51, one 52, one 53, two 54, one 57, one 59, and one 71. Nine were females and one a male, the male being the oldest, 71. These cases had arthritis from five months to 12 years until the time of consultation. One case for 3 months, one for five months, one for two years, one for four years, one for five years, one for seven years, three for 10 years, and one for twelve years.

In all these cases ages or length of time of arthritis made no difference regarding the sensitization to foods as to the number of foods to which sensitized or changes to sensitization at different tests.

In case 1, reactions were obtained to rice in test 1 and 2 but not in the other four cases, while oatmeal gave reactions in the 4th and 5th tests but not in the other tests. Corn gave reactions in test 2 and 6 but not in the other tests while in case 2 oatmeal gave reaction in the 1st and 3rd tests but not in the others. Though rice gave reactions on the 5th test and corn in the 6th, neither one of them showing a reaction in the other tests. In case 3, white flour gave reaction in the 1st test, corn in the 5th test, neither one showing in four tests. Case 4, rice gave reaction in the 3rd test, and no other cereal showing in two different tests, while case 5 showed no reaction to cereals in two different tests. Case 7 gave reactions in oatmeal in the 3rd test, but not in the other two. Corn gave reaction in the 1st and 2nd test, and soy bean flour showed in the 3rd test. In case 8, reactions obtained to rice in tests 1 and 4, corn in 2, and oatmeal in the 3rd test. Case 9 gave reaction to oatmeal and rye in the 1st test, and to oatmeal in the 2nd test. Here is seen a reaction to oatmeal in both tests. In case 10, oatmeal showed in tests 1 and 2, rice in 3, white flour in test 2, and rye in test 3, and corn in test 1.

Poultry:

The following reactions were obtained to meats: Case 1 chicken was positive, in tests 1, 2, and 3 but not in the following three tests. Chicken in case 2 gave a reaction in test 1 but not in the other five tests, while in case 3 chicken gave reactions in test 1, 3, and 4, but not in 2 and 5. In cases 4, 5 and 6 which cases were tested nine times there were no reactions to chicken, while in case 6 reactions were obtained to turkey in the 3rd test. In case 7 chicken gave reaction at the 1st and 2nd test but not at the 3rd. In case 5 chicken gave reaction at the 1st test but not the other four, and turkey gave a reaction on the second test. Case 9 chicken gave reaction the 1st test but none the 2nd test. In case 10 chicken shows a reaction in the first test but not the other two tests.

Beef:

Case 1 beef gave reaction to test 1, 2, 5, and 6 but not in the other two. In case 2 we have reaction to beef in test 2, 5 and 6. Case 3 gives a reaction to beef in test 1 and 5 but not the other three tests. Case 4 gives reactions in tests 2 and 3 but not in 1. Case 5 gives a reaction in test 2 but not in 1. In case 6 beef shows reaction in test 3 but not in the others while veal gives reaction in test 1. Case 7 no reaction obtained to beef.

Case 8 beef gave reaction in test 2 while not in the other four tests while veal gives reactions in test 5. Case 9 beef shows reaction in the second test but not in 1 while in case 10 beef gave reaction the second test but not the other two.

Case 1 gives a reaction in the second and sixth tests to lamb but not in the other four tests. Reactions to beef were also obtained in these two tests, but none to lamb in the fifth test, when beef gave a reaction. Of the 16 tests made in case 2 and 3, 5 and 7 no reactions were obtained to lamb, while of 17 different testings in cases 4, 6, 8, 9, and 10, lamb gave a reaction five times, that is once in each of these cases.

Pork gave a reaction in case 2 in the 4th test. Case 5 in the 1st test. Case 6 in the 4th test. Case 8 in the 3rd and 4th tests. In case 8 lamb and pork both show at the same test.

Thus are shown reactions obtained to cereals, fowl, and meats in the different tests, and their absence in other tests in these cases. The results sustain the contention that there are no definite changes in sensitivity to foods in the various tests in each individual case. Regarding the other classes of foods, a few illustrations may be given to explain what is meant by changes in sensitization, or degree of allergic response at different periods.

Case 1 at the 3rd test gave a reaction to milk. Reactions were obtained to milk in case 2, in the 3rd and 4th tests; in case 4, the 2nd test; case 5, the 2nd test; case 8, the 5th test.

Egg Tests:

Reactions to whole egg were obtained in case 1, 3rd test; case 2 the 1st and 2nd test; case 3 in the 3rd test; case 6 in the 4th test. While egg yolk gave reaction in case 2 at the 4th test, there was a reaction to the whole egg in tests 1 and 2. Egg yolk gave a reaction in case 5 and 2nd test; egg white showed in test 1 of this case; while in the 6th case, egg yolk gave reaction in test 2 and egg white in test 1. In case 7, egg yolk gave a reaction in test 3, and egg white in test 2. Here in some cases the whole egg gives reaction, while in others only the egg white may show, while others still have a reaction to egg yolk, or vice versa when the egg yolk shows and not the egg white.

Fish:

Case 1, haddock gave reaction in the 1st, 2nd, and 3rd tests. Case 2 showed reaction in the 4th test, there being no reaction to haddock in the 4th and 5th cases while haddock gives a reaction in case 6 test 2. No reaction with haddock in case 7, in case 8 obtained a reaction in the 3rd test. Case 9 reaction to haddock in the 1st test.

Potatoes:

Case 1 shows a reaction to white potato in the 5th test. In case 2 in the 6th test proved no reaction to potato. Case 3 gave reaction to white potato in test 3 and sweet potato in test 2. Case 4 shows reaction to potato in test 1, but case 5 shows no reaction to potato. Case 6 gives a reaction to white potato in the 2nd test and sweet potato in the 3rd test. No reaction to potatoes in case 7. Case 8 gives a reaction to potato in the 1st and 4th tests, while case 9 and 10 give no reaction.

to potato, while a reaction is obtained to both white and sweet potato in case 3 in the 1st and 2nd tests. Reactions were obtained to both of these potatoes in case 6 in the 2nd and 3rd tests. Although no reaction was obtained to sweet potato in cases 1, 4, 8, which gave reactions to white potato.

Citrus Fruits:

Orange, no reaction in case 1, 3, 7, 9, while reactions were obtained to orange in case 2, 3rd test; case 4, 2nd test; case 5 at each test; case 6, 2nd test; case 8, 2nd test; and case 10, 2nd test.

Grapefruit is nonreactive in cases 1, 2, 4, 5, 6, 8, 10, while grapefruit shows a reaction in case 3, test 1, 2 and 3, but not in the other two tests made in this case. Grapefruit gave a reaction in case 7, 3rd test and case 9, 2nd test.

Lemon gave a reaction in case 3 on the 5th test. Grapefruit gave reactions in case 3 in test 1, 2 and 3, although on test 4 there was no reaction to any of the citrus fruits. Lemon gave reaction in case 8 at the 4th test, while the orange was the only other citrus fruit in this case which gave reaction on the 2nd test. Thus we see that in all these tests, the three citrus fruits, orange, grapefruit and lemon, have not, at any one time, or in any one case, shown a reaction to all of these in any one test or any one case.

In looking over these discussions regarding the different reactions to different foods, one may see by glancing at the table, *Foods to which patients are sensitive at different times*, that within the individual's constitution, there can be a change in sensitivity to certain foods, to which he might become gradually and definitely allergic after a considerable lapse of time between tests. No explanation is here attempted, but rather the effort to record the results of carefully conducted tests.

CONCLUSIONS

1. Foods are a factor in arthritis cases.
2. Changes in cutaneous reactions to foods to which a patient is allergic can take place.
3. The interval of time elapse between tests of these arthritic cases varied from one year one month to eight years and eight months.
4. The time of relief between symptoms varies from one year one month to eight years and four months.
5. The average relief from symptoms being two years and four months.

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The Role of The Fat Soluble Vitamins A and D in Nutrition

Continued

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THE EXTENT OF VITAMIN A DEFICIENCY AS DETERMINED BY VISUAL ADAPTATION

BY MEANS of a photometer, Jeans (*Jeans, P. C. Vitamin Deficiency in Childhood, Minnesota, Med. 16:688, Nov., 1933*) showed the large percentage of children in whom diminished visual adaptation was present as an indication of vitamin A deficiency. His work was conducted as follows: The child was first put in a dark room for ten minutes, then the child was exposed to bright light for three minutes. During the next ten minutes, the child's visual adaptability was again tested. Recovery with improvement in visual adaptability resulted from the administration of ample amounts of vitamin A over a period of several weeks. Although the work has been criticized and the increased adaptability blamed on the practice resulting from repetitions of the test with the photometer, this of course does not alter the fact of the therapeutic significance of the administration of ample amounts of vitamin A in the rehabilitation of visual adaptability.

Jeans and his co-workers (*Jeans, P. C. and Zentmire, Z. The Prevalence of Vitamin A Deficiency Among Iowa Children. J. A. M. A. 106:996-997, 1936*) (*Jeans, P. C., Blanchard E. and Zentmire, Z. Dark Adaptation and Vitamin A. A New Photo-*

metric Technic. J. A. M. A. 108:451-458, 1937) found that 26 percent of a group of children in the rural districts and 53 percent of a village group of children in Iowa showed evidence of vitamin A deficiency as determined by the photometric test for dark adaptation. In an urban group of children, the percentage varied between 56 and 79 percent depending on the economic level. Normal dark adaptation developed when given ample amounts of vitamin A. Halibut liver oil and carotene in oil were the sources of vitamin A that were used.

Moreover, Getz, Hildebrand and Finn (*Getz, H. R. Hildebrand, G. B. and Finn, M. Vitamin A Deficiency In Normal and Tuberculous Persons, As Indicated by the Biophotometer. J. A. M. A., 112:1308-1311, 1930*) found a shortage of vitamin A in one out of every ten apparently normal individuals. The deficiency in vitamin A was found to be particularly serious in the tuberculous. In a series of tuberculous and non-tuberculous individuals exhibiting evidence of vitamin A deficiency by means of the biophotometric test, cure of the condition was obtained by the administration of massive doses of vitamin A in the form of halibut liver oil. In a group of six persons in whom 20,000 units a day of vitamin A in halibut liver oil failed to produce any amelioration of the condition, cure of the

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deficiency in some of these cases was obtained by the administration of 90,000 units a day. In those cases where even this amount failed to produce a sufficient reaction, 200,000 units of vitamin A per day in the form of halibut liver oil was successful. This amount was continued daily until a favorable response was noted and the dose was then reduced to 100,000 units a day or less.

Four individuals were given 2,000,000 units of vitamin A per day in the form of halibut liver oil. Except for a dull headache, there were no other pathologic effects.

Further evidence of the prevalence of vitamin A deficiency was shown by Jeghers (*Jeghers, Harold. The Degree and Prevalence of Vitamin A Deficiency in Adults with a Note on Its Experimental Production in Human Beings. J. A. M. A., 109:757, Sept. 4, 1937*). He examined 162 medical students for evidence of vitamin A deficiency through a study of the dark adaptation test by means of the biophotometer. Thirty-five percent showed photometric evidence of vitamin A deficiency; in addition another twelve percent showed clinical evidence of such deficiency. The cause was to be found in the eating habits of the students which was similar to that of other adults in the general population. Although even the worst of these diets contained about 1,000 units of vitamin A daily, it was definitely below the normal requirements necessary to eliminate clinical evidence of any disturbances due to vitamin A deficiency. Every student with one exception who had sinusitis showed a normal dark adaptation if his diet included a daily intake of 4,000 International Units. A fifty percent increase above this amount is recommended in order to obtain optimal advantages. This of course, applies to adults under normal conditions.

Striking results were obtained in the cure of students exhibiting hemeralopia. Vitamin A in the form of halibut liver oil was added in addition to milk, butter, fresh fruits and vegetables. The best results were obtained after the daily oral administration of 70,000 units of vitamin A for two weeks, followed by the daily administration of 25,000 units of the vitamin until the condition was cured.

Maitra and Harris (*Maitra, M. K. and Harris, L. J.: Vitamin A Deficiency Among School Children in London and Cambridge, Lancet 2:1009-1014, Oct. 30, 1937*) showed the frequency of vitamin A deficiency particularly among the underprivileged. In the examination of 193 children among the poor there was evidence of a vitamin A deficiency varying from twenty-two to thirty-six percent. Compared with the results obtained in the examination of the underprivileged children was the fact that among 30 boys educated in English private schools, not a single case of vitamin A deficiency was found.

In the examination of a group of 22 adults whose ages varied between 20 and 50, they found only five cases exhibiting a definitely subnormal state. In a group of 38 mothers of the elementary school children whose ages ranged between 25 and 35 not a single case of a definitely subnormal state of vitamin A de-

ficiency was found. In both of the groups of adults however, and also among the better nourished group of children there were a number of cases exhibiting a moderate degree of hypovitaminosis A.

Eight drops of halibut liver oil or three teaspoons of cod liver oil daily for two to four weeks produced striking changes in practically all of the cases showing evidence of vitamin A deficiency.

Those children showing mild evidence of vitamin A deficiency became normal when treated with six drops of halibut liver oil a day for two weeks.

Other Disturbances of the Eye Due to Vitamin A Deficiency

Kruse (*Kruse, H. D. Methods of Detecting Mild Cases of Vitamin A Deficiency, Science 95:623, June 19, 1942*) stated that in many individuals who showed no impairment of visual adaptation, evidence of vitamin A deficiency could be demonstrated by gross or microscopic changes in the conjunctivae which disappeared following the administration of vitamin A.

In man serious changes in the eye as a result of the deficiency of vitamin A, other than those directly related to light perception, have been studied with great care. In the canthi small patches develop resulting from cornification of the epithelium and bacterial proliferation (Bitot's spots). The cornea as a result of infection may be completely destroyed. The conjunctival epithelium also becomes infected and undergoes destruction. Pillat has described pigmentation of the eye apparently related to melanin as an evidence of vitamin A deficiency. (*Pillat, A. Does Keratomalacia Exist in Adults? Arch. Ophth. 2:256, 399, 1929*).

When the vitamin A potentialities of the organism are exhausted and there is no replenishment, the animal loses weight, and becomes sickly. Many of the animals then develop serious eye disease. The lids become swollen. There is increased sensitivity to light. Soon there is a catarrhal inflammation of the conjunctivae. The discharge becomes purulent and bloody, the lids sticky and the eye closed. Eventually the cornea is also affected and blindness sets in. Before the final stages of the disease, however, cure is possible by the administration of adequate quantities of vitamin A. In this manner the vitamin A potency of any food may be determined, and experimentally accurate quantitative gradations of vitamin A content may be established as measured by the effect of the food to be tested on the rate of growth of the animal.

Early History of Xerophthalmia

Historically, the role of vitamin A deficiency in the development of xerophthalmia is of considerable interest. Among the earliest descriptions of xerophthalmia is that of Fischer in 1846 and of Arlt in 1851, although the first minute description of the disease was that of Albrecht v. Graefe in 1866 (*Blegvad, O. Xerophthalmia, Keratomalacia and Xerosis Conjunctivae. Am. J. Ophth. 7:89, 1924*). In that year Gama Lobo described keratomalacia in Brazilian children. He believed the condition to be one of cellular atrophy due to bad nutrition. He called the disease "ophthalmia Brasiliana." The earliest signs of xerophthalmia were described by Bitot in 1863, on the basis of a study of

twenty-nine cases which occurred in a foundling hospital in Bordeaux. Similar descriptions of xerosis conjunctivae as well as hemeralopia and the more severe cases of keratomalacia were described by Blessig in Petrograd in 1866. He noted that the disease occurred most commonly during the lenten season and he attributed the disorder to a disturbance of nutrition because of the fasting.

Mori noted that although the disease was not uncommon in children, it was practically unknown on the coast where good fish was available. Schiele in 1907 also noted among the cases of keratomalacia in Russia that cod liver oil was curative.

The treatment of hemeralopia with liver has been known since early antiquity and is recommended as a therapeutic measure in "Eber's Papyrus" (1500 B. C.). The use of raw ox liver was recommended by Hippocrates. Treatment of xerophthalmia with liver was also common in Japan and China.

There is ample clinical evidence of the seriousness of vitamin A deficiency as a result of food shortages during various periods in history. One of the most serious was that which developed in Denmark during the first World War. Owing to the insistent demand of the Germans for butter-fat from the Danes, the infants in Denmark received only skimmed milk. Since the vitamin A is present in the butter fat of the milk, these infants being deprived of this essential vitamin, showed a high mortality rate (21%). Blindness was common and many of the infants that survived showed permanent evidence of the effect of the deficiency.

The Effect of Vitamin A Deficiency on the Mucous Membrane

Wolbach and Howe (*Wolbach, S. B. and Howe, P. E. Tissue Changes Following Deprivation of Fat Soluble A Vitamin. J. Exper. Med., 42:573, 1925*) in their histopathologic studies of the effect on the various tissues resulting from deprivation of vitamin A showed that the essential lesion was a replacement of the various epithelia by stratified squamous keratinizing epithelium. He found these changes to occur in the nares, the nasal septum, the larynx, trachea and bronchi.

Similar changes were noted in the submaxillary glands, the parotid glands, the accessory salivary glands and at times in the pancreatic ducts. The stomach, liver, the small and large intestine were not affected. In the genito-urinary tract the changes were noted in the bladder, ureter, pelvis of the kidney, in the uterus and oviducts, the epididymis, prostate, and seminal vesicles. The epithelium of the kidney and of the seminiferous tubules is not affected.

Epithelial changes were noted in the conjunctiva, the ducts of the Meibomian glands, the cornea, lacrimal gland, Harderian gland and the extra orbital gland. The thymus showed small cysts filled with desquamated keratinized epithelium.

As a result of these changes, there is a disturbance in the functional behavior of the affected regions. Because of the loss of cilia, the trachea is not properly cleared of extraneous material. In addition, the substi-

tuted epithelium is less resistant to warding off infection. Vitamin A deficiency may thus lead to an impairment of "the body's first line of defense" in resisting infection. A similar result takes place in the conjunctiva because of the destruction of the cells which secrete mucus. The metaplasia also leads to an occlusion of the ducts leading from the involved glandular structures. This results not only in an inability of the involved gland to carry on normal secretory functions but also makes it susceptible to infection.

Inflammatory lesions of the alimentary tract and of the urinary tract were described by Mellanby (*Mellanby, E. Nutrition and Disease. London, Boyd and Oliver, 1934*) as occurring in many of the experimental animals maintained on a diet deficient in vitamin A.

Mellanby found the following distribution of lesions in young rats maintained on a vitamin A deficient diet. The larger percentage showed infection of the genito-urinary tract, including pyelonephritis, cystitis, renal and bladder calculi, hydronephrosis as well as dilatation of the ureters and distention of the bladder. The next common complication was the development of abscesses in the floor of the mouth with suppurating glands in the neck. Next in frequency was xerophthalmia. In addition some of the animals showed acute inflammatory changes of the stomach, the small and large intestine, disease of the middle ear and nasal sinuses.

An analysis of clinical evidence indicated that when the diet was devoid of vitamin A or carotene, human beings also developed lesions similar to those in the experimental animals. In the presence of deficiency of vitamin A, human beings may be more susceptible to certain types of infection. Under such conditions of a vitamin deficient state their resistance to infection may be increased by the addition of vitamin A to the diet.

Evidence of the deleterious effect of vitamin A deficiency in the alimentary tract has been shown by the experiments of Tilden and Miller on monkeys. Such injurious effect often proved fatal before any gross evidence of damage to vision (*Tilden, E. B. and Miller, E. G., Jr. The Response of the Monkey (Macacus Rhesus) to Withdrawal of Vitamin A from the Diet. J. Nutrition 3:121-140, 1930*).

Tilden and Miller kept monkeys on a practically completely vitamin A deficient diet and at autopsy found a diseased condition of the intestine. The severity of the disorder varied in different cases. Although gross lesions of the intestine were rare, in two cases there was a small area of ulceration of the colon. Histologic study showed the presence of a severe ulcerative colitis, the ulcers being demonstrable only by microscopic study. It is interesting to note that there was an absence of xerophthalmia, although this is one of the lesions most readily produced in some animals when vitamin A starved. Evidence of epithelial metaplasia in some of the organs, however, such as the trachea and salivary glands was found. Because of the delicacy of the monkey as compared with the rat it is possible that the monkey dies of the intestinal disease

long before there has been an opportunity for the development of the eye lesion.

Manville also studied the effect of vitamin A deficiency on the mucosa of the alimentary tract and showed a marked reduction in the number of goblet cells. As a result of the diminution in the amount of mucus secretion, the mucosa of the alimentary tract became predisposed to injurious effects produced by the irritation of the food with capillary bleeding. Thus the finding of occult blood in the stool might be an early manifestation of a vitamin A deficiency state (*Manville, I. A. The Interrelationship of Vitamin A and Glycuronic Acid in Mucin Metabolism. Science 85:41, 1937*).

Skin Manifestations Resulting from Vitamin A Deficiency

Among the various changes that have been described as resulting from vitamin A deficiency are those found in the skin. The skin at first is dry and slightly rough, followed by the sudden appearance of eruptive lesions in localized areas. The lesions first appear on the antero lateral aspect of the thighs or in the postero lateral region of the forearms then spreading to other regions. The lesion on the face resembles acne. This skin lesion described by Frazier and Hu was amenable to vitamin A therapy with improvement in the secretory function of the skin and the gradual disappearance of the eruptive lesion.

A further indication of the relationship of vitamin A to this type of skin lesion is indicated by the fact that it was frequently associated with the classical ocular manifestation of the disease. Both these lesions disappear with vitamin A therapy. The main type of cutaneous lesion was the keratotic follicular papule. In addition there were other evidences of excessive keratinization in the form of warty plaques on the knuckles and ankles.

Histopathologic studies were made of specimens of the skin lesions. These showed that the pathologic process was essentially due to increased keratinization of the epithelium of the hair follicles. As a result there was an obstruction of the hair follicles. The damaged follicles showed a moderate infiltration with lymphoid cells. The minute skin changes appeared to be similar to those occurring in the tissues of the eye as a result of vitamin A deficiency. The skin lesion was most common in those over fifteen years of age and infrequent in younger individuals (*Frazier, C. N. and Hu, C. Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency. Arch. Derm. and Syph. 33:825, 1936*).

In addition to the changes in color of the conjunctivae, due to an increase of the melanin, Pillat (*Pillat, A. Does Keratomalacia Exist in Adults? Arch. Ophth. 2:256, 399, 1929*) also observed peculiar grayish yellow discoloration of the skin in some of his vitamin A deficiency patients. The skin in addition is rough and dry and in severe cases gave the impression as if the skin had been dusted with a coarse powder. Scaling is present in some cases. The roughness of the skin was due to the lack of sebum as well as to the pres-

ence of horny cells in large numbers. The skin may be edematous and swollen. Because of the lack of sebum, the skin may be covered with hundreds of comedones. Secondary infection of the comedones and hair follicles frequently occurs and leads to the development of follicular abscesses, similar to the condition found in simple acne.

"In cases in which nourishment rich in vitamin A is given, these abscesses and the deepest pockets dry up in wonderfully short time without any surgical treatment." Pillat also noted extreme dryness of the hair in these cases with the scalp covered with dandruff. The hair showed a tendency to become gray and fall out. The nails showed furrows which peeled off in small particles.

Straumfjord (*Straumfjord, John V., Lesions of Vitamin A Deficiency, Northwest Medicine 41:7, 229, July, 1942*) "observed in a large number of patients the effect upon various clinical conditions of a daily oral intake of 100,000 units of Vitamin A. A large number of patients with follicular hyperkeratosis have been followed, many over a period of four years. . . . The response to Vitamin A administration is extremely variable. In some patients the lesions disappeared in a few months, while in others they are still present, although greatly diminished after a four year period of continuous daily oral intake of 100,000 units of Vitamin A."

The relationship of vitamin A deficiency to lesions of the skin is also suggested by the work of Rapaport, Herman and Lehman (*Rapaport, H. G., Herman, H. and Lehman, E. Treatment of Ichthyosis with Vitamin A. Jour. Pediatrics 21:733, Dec., 1942*). They treated six patients with ichthyosis by means of the oral administration of 60,000 to 200,000 International Units of vitamin A per day over a period of several months. Some of the patients also received 100,000 units of vitamin A injected intramuscularly two or three times a week over a period of several months.

Improvement was reported in the condition of the skin lesion. The texture of the skin became more normal, with disappearance of cracks and fissures as well as a marked diminution of pruritis. An impaired dark adaptation which was coincidentally present also showed marked improvement with the vitamin A therapy.

The Teeth as Affected by Vitamin A Deficiency

Wolbach and Howe have described metaplastic changes of the enamel organ with replacement by stratified squamous epithelium. Because of the destruction of the normal enamel, the teeth assume a chalky appearance produced by the dentin. Apparently it is the incisor teeth which are most seriously involved as a result of the deficiency state.

Orten, Burn and Smith (*Orten, A. N., Burn, C. G. and Smith, A. H. Effects of Prolonged Chronic Vitamin A Deficiency in the Rat With Special Reference to Odontomas. Proc. Soc. Exper. Biol. and Med. 36:82, 1937*) showed that the incisor teeth as a result of Vitamin A deficient diet developed a progressive loss of the normal orange pigment, with opacity and

distortion of shape. In those animals that died, the cause in most cases was tracheal obstruction from a mucopurulent plug. They were also found to have evidence of otitis media, sinusitis and calculi in the urinary bladder.

Most of the animals that survived 365 days on a low vitamin A diet, not only showed changes in the incisor teeth, but also tumor growth (odontomata) replaced the alveolar structures of the upper and lower jaws. Most of the incisor teeth were distorted or replaced by these tumor growths.

Renal Calculi and Vitamin A Deficiency

The formation of renal calculi in the experimental animal has been attributed to a diet deficient in vitamin A (Steiner, M., Zuger, B. and Kramer, B. *Production of Renal Calculi in Guinea Pigs by Feeding Them a Diet Deficient in Vitamin A. Arch. Path.* 27:104, 1939). Steiner, Zuger and Kramer showed that in guinea pigs, on a vitamin A deficient diet, autopsy revealed changes in the urinary tract. The ureters were enlarged and thickened in thirty-one of the thirty-five animals that had survived for more than fourteen days. These alterations were due to thickening and reduplication of the mucosa. Desquamation of the epithelium was a common finding. In nine of the thirty-five animals there were calculi in the ureter or renal pelvis. The first microscopic evidence was a hyperplasia of the ureteral mucosa. This was followed by a metaplasia of the mucosa to a stratified keratinized epithelium. The large plaques of desquamated epithelial cells acted as foci for the development of calculi. The inorganic material of the calculus was calcium carbonate. Wolbach, however, doubts the etiologic relationship and believes that factors other than the absence of normal amounts of vitamin A are responsible for this development. When such calculi do occur in the experimental animal, it is believed that they form about masses of desquamated epithelium resulting from the metaplastic process. There is no proof at present that vitamin A has any effect on the occurrence of renal calculi in man.

Jewett, Sloan and Strong (Jewett, H. J., Sloan, L. L. and Strong, G. H. *Urolithiasis. J. A. M. A.* 121:566-568, Feb. 20, 1943) studied twenty patients with urolithiasis for evidence of vitamin A deficiency by means of the dark adaptation method as well as the vitamin A content of the blood.

In addition the respiratory and urinary tracts were examined at autopsy in seventy-eight patients with urolithiasis for evidence of epithelial metaplasia. They showed that there was no evidence to indicate that in the human being vitamin A deficiency was present in urolithiasis.

Pregnancy and Vitamin A

The possible role of pregnancy in being associated with a diminution in vitamin A is indicated by the work of Edmond and Clemmesen (Edmond, Carsten and Clemmesen, S. *On a Deficiency of A Vitamin and Visual Adaptation*, London, Oxford Univ. Press, 1936). They showed on the basis of disturbed visual adaptability that about fifty percent of pregnant women

in Copenhagen municipal hospital suffered from vitamin A deficiency.

In addition to the evidence of disturbed visual adaptation in pregnancy, it was also detected in women who had recently given birth and in cases of hepatitis. Excluding pregnancy and organic eye disease, they found evidence of vitamin A deficiency by the dark adaptation method in five to six percent of the usual run of medical patients.

They stated that evidence of the effectiveness of the intramuscular administration of vitamin A containing liver oil preparations could be noted in a couple of minutes, and after oral administration in less than twelve hours.

A more serious relationship of vitamin A deficiency to the reproductive function has been indicated by Evans and Bishop (Evans, H. M. and Bishop, K. S. *On An Invariable and Characteristic Disturbance of Reproductive Function in Animals Reared on a Diet Poor in Fat Soluble Vitamin A. Anat. Rec.* 23:17, 1922). On a diet poor in vitamin A, they showed that among the earliest manifestations even in the presence of good growth and apparent health, the experimental rat suffers from an abnormality of the ovaries, as determined by histological changes in the vaginal smear. These changes can be correlated with the growth maturation and rupture of the Graafian follicle. On diets low in vitamin A and yet nevertheless ample enough to permit normal growth there is an interference with the ability of the Graafian follicles to mature and rupture. These abnormalities may be detected from a study of the vaginal smear showing the development of cornified epithelial cells.

A possible relationship of vitamin A deficiency to sterility was shown by Evans (Evans, H. M. *Testicular Degeneration Due to Inadequate Vitamin A in Cases Where Vitamin D is Adequate, Am. J. Physiol.* 99:477, Jan., 1932). He maintained male rats on diets low in vitamin A but adequate in vitamin D and found that they became sterile in three months. Histologic study of the tests showed the cause of the sterility to be due to the development of marked degenerative changes.

Mason (Mason, K. E. *Foetal Death, Prolonged Gestation and Difficult Parturition in the Rat as Result of Vitamin A Deficiency. Am. J. Anat.* 57:303, 1935) showed that the method of examining the vaginal smear for a determination of vitamin A deficiency is much more sensitive than that of either retardation of growth or the development of xerophthalmia and that evidence of cornification of the vaginal smear occurs long before either of these two manifestations. The value of the method lies therefore in the fact that comparatively mild degrees of vitamin A deficiency may be definitely determined.

When pregnant rats were kept on a low vitamin A intake and the vaginal cornification persisted throughout pregnancy, the animals frequently failed to come to term. This reproductive disturbance could in the majority of cases be eliminated after the inclusion of ample vitamin A. Pregnancy then was normal as to term and delivery.

The severity of the disturbance in the reproduction process as a result of vitamin A deficiency can parallel to the severity of the vaginal cornification. When the death of the fetus occurred in vitamin A deficient rats, this was due to changes in the uterine epithelium with secondary infection of the maternal decidua and of the wall of the uterus. Pronounced vitamin A deficiency during pregnancy may lead to death in utero and resorption, due to the fact that the maternal decidua becoming necrotic, the nutrition of the fetus is seriously interfered with. The cornification of the vaginal epithelium may increase the difficulty of labor.

Based on the fact that vitamin A is important in the maintenance of the normal structure of the vaginal epithelium, Simpson and Mason (*Simpson, J. W. and Mason, K. E. A New Concept of Senile Vaginitis. Am. J. Obst. and Gyn. 32:125, July, 1936*) treated cases of senile vaginitis by the administration of vitamin A in the form of liver oil. An improved state of the vaginal epithelium occurred in those cases in which there had previously been a dietary deficiency of vitamin A. In thirty cases of senile vaginitis which were observed, the addition of the increased amounts of vitamin A in the form of fish oils was followed not only by repair of the vaginal epithelium but also by relief of symptoms.

Vitamin A and the Nervous System

Mellanby (*Mellanby E. Nutrition and Disease, London, Royd and Oliver, 1934*) noted the nutritional influence of vitamin A deficiency on the nervous system of young dogs. These animals showed evidence of incoordination and stiffness of the hind legs which ultimately became very weak. In addition, the animals appeared as if dazed and mentally affected. By the addition of such sources of vitamin A as fish liver oil,

these changes could be prevented. Even after the incoordination had developed, marked improvement might result from the addition of vitamin A to the diet. Not only was the pathologic process in the nervous system arrested but some degree of cure was also possible. The evidence of changes in the spinal cord was substantiated by histopathologic studies.

That the effects of a vitamin A deficiency state in producing degenerative changes in the spinal cord was not limited to the dog was indicated by the fact that similar findings were obtainable when the experimental animals were young rabbits, rats and birds.

Varying degrees of demyelination in the optic nerve and the trigeminal nerve were also noted when the diet was deficient in vitamin A.

In some cases of retro-bulbar neuritis in children cure was obtained through the addition of the vitamin A of fish liver oil.

Disturbances in the nervous system due to vitamin A deficiency have been described in the experimental animal by Irving and Richards (*Irving, J. T. and Richards, M. B. Early Lesions of Vitamin A Deficiency. J. Physiol. 94:307, 1938*). Of 141 rats fed on a vitamin A free diet 108 showed degenerative changes in the medulla. In those animals in which no such changes were found, the reason seemed to be that they were killed too soon after being on this diet. Some of these pathological changes occurred in animals killed at a time when growth and apparent health were still maintained. Thus subtle degrees of vitamin A deficiency might be responsible for organic changes in the nervous system. A comparable group of animals on a vitamin A free diet to which adequate amounts of carotene or vitamin A had been added showed no such pathologic changes. (To be continued in July 1944 issue)

Hypoglycemic Reaction With Convulsions In Ascariasis (Case Report)

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I HAD the opportunity to see the case of a young boy whom we first were inclined to classify as hypoglycemic epilepsy (1). The case-report is in brief as follows:

J. R. S., age 9. Family history irrelevant. First convulsion at the age of 8 months when he had bronchial pneumonia. Since then, he had several attacks of convulsions when he had fever. Now and then a round worm was passed. No pathologic findings on the first physical examination. Presence of phimosis was noted. On December 1, 1942, he was brought to the hospital again. He now and then in the meantime had been complaining of sick spells with choking in the throat and excessive thirst which forced him to drink, for weeks, large amounts of water. He had a craving for

food all the time, and turned pale each time when he could not satisfy his hunger at once. The boy reported that he always felt the spells coming; they were more prone to recur after exertion. The day before admission he vomited, then turned pale and moaned; finally, he went into a convulsion with jerking of arms, loss of consciousness, rolling of eyes upward, rigidity of the body, and opisthotonos. This fit lasted for about five minutes. He felt drowsy and sleepy thereafter. There was another similar spell in the evening on the day of admission. Physical examination again did not reveal any evidence of organic disease. Sella turcica was of normal appearance on x-ray. No scars or evidence of previous tongue-bites found. No increase of urinary output in 12-hour period. Blood sugar (venous blood, method of Folin-Wu) fasting A. M.: 85 mgs. %, before noon 50 mgs. %.

In the weeks following the boy passed six ascaris. On rechecking in January 1943, the blood sugar, fasting A. M., was 125 mgs. % and was found to be the same in August 1943. The boy then had gained 5½ pounds. There were no convulsions any more, and general condition was very satisfactory. The same satisfactory condition prevailed in November 1943, with further gain in weight, absence of ova in the stool, and fasting blood sugar 90 mgs. %.

Evaluation of the signs and symptoms described had to take several heterogenous conditions into consideration.

Intoxication by toxic substances produced by the round-worms in the different organs (4, 5, 6, 16).

Functional hepatic disorder resulting from temporary depletion of glycogen-reserve (2).

True epilepsy, or at least, symptomatic epilepsy (11).

True organic hyperinsulinism.

Functional hypoglycemia due to endogenous factors (2) e.g. pituitary insufficiency (3) Addison's disease.

We felt that the primary and central signs and symptoms in the case under discussion were the ascariasis, the convulsions, and the hypoglycemia, the latter being present at the time of the convulsions. From the clinical course, we feel justified in bringing these signs and symptoms in causative interdependence from each other and to disregard all other possibilities listed above as being either secondary or non-existent.

The peculiar trias of ascariasis, hypoglycemia and convulsions in this case was so impressive that we undertook to study the literature in order to find out whether or not this clinical picture already has been described. We could not find it mentioned anywhere, and we are greatly indebted to Dr. Hugh Headlee, Assistant Professor of Parasitology, Indianapolis, Indiana, whom we contacted and who kindly informed us that he too could not find any mention of hypoglycemia in connection with ascariasis.

Spontaneous hypoglycemia has been referred to organic or functional irritation of the Langerhans Islands (7). An elaborate list of the causes of spontaneous hypoglycemia is given by Duncan (12). A rather recent paper (8) contributes hypoglycemia to the following possible causes:

1. True hyperinsulinism
2. Relative hyperinsulinism
3. Renal glycosuria
4. "Cryptogenetic"

In the presence of convulsions in spontaneous hypoglycemia, certain conditions have to be ruled out first: "Acute infection, chorea, tetany, syphilis, cerebral defects, brain tumor, birth injury, meningitis poliomyelitis" (8). None of these conditions were present in our case.

Ascariasis as the cause of functional hypoglycemia with convulsions is not mentioned by any one of the authors. As there is no evidence in our case of true hyperinsulinism or renal glycosuria, it must be put under the heading of either relative hyperinsulinism or cryptogenetic.

We are not able to state definitely whether our case

belongs to the group of relative hyperinsulinism or rather should be branched off from the cryptogenetic group as a clinical entity. Also, the mechanism of hypoglycemia reaction with convulsions in ascariasis is not yet clear. W. H. Headlee (6) suggested several possibilities to be considered:

1. The low blood sugar-level may have been purely incidental and irrelevant as it is known that a blood-sugar-level of 50 mgs. % may be present in children without causing any marked symptoms. This is corroborated by Evans and Allen (13).

2. The convulsions may not have been due to the low blood sugar-level, but may have been the result of the action of toxins liberated by the worms. The worms, per se or by their toxins may have disturbed the organs of digestion, liver and endocrine glands sufficiently and in a manner to have resulted in the low blood sugar.

3. The hypoglycemia might have been caused by some factor outside the realm of the ascariasis infection. I might add the following possibilities:

4. The low blood sugar may be the effect of a sub-clinical hepatitis with consecutive disturbance of the carbohydrate metabolism. We know from the literature that ascariasis may cause hepatitis (14) and enlargement of the liver during the migration of the larvae (15).

5. There is experimental evidence that drugs which stimulate the parasympathetic nervous system, produce a fall in the blood sugar (9). Portis and Zitman on the basis of their own experiments came to the conclusion that continued vagal stimulation in the psychoneurotic patient is an important factor in producing functional hyperinsulinism and concomitant hypoglycemia. The latter results from emotional processes being relayed through the hypothalamus to the autonomic nervous system (10). It may be assumed, then, that the toxins contained in the round-worms (4, 6) act in the same way by producing hypoglycemia through stimulation of the parasympathetic nervous system.

The case presented seems at least to justify the opinion that ascariasis should be listed as a possible cause of functional hypoglycemia leading to convulsions. Furthermore, our case seems to verify the impression that the term "hypoglycemic epilepsy" may be misleading because it invites us to classify patients with convulsions associated with hypoglycemia as epileptics while close observation may detect such an innocent cause as ascariasis and bring about cure of the whole syndrome by removal of the worms.

Experimental studies with extracts from round-worms in regard to their action upon the blood sugar-level of animals may be able to clarify the problem under discussion and to contribute to our still rather vague knowledge of the mechanism of functional hypoglycemia.

SUMMARY

A case of ascariasis with convulsions and hypoglycemia is presented. The possibility of this trias being a clinical entity is discussed. Certain hypotheses are given of the mechanism involved.

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Regional Enteritis

By

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THIS relatively new disease is being seen more commonly and the accuracy of diagnosis is well represented in the case to be reported, in that, in spite of the fact that the patient had multiple conditions the true nature of the situation was well understood and

There had been a tendency to constipation. He had lost his appetite and during the period from November, 1942 until February 15th, 1943, at which time he was first seen by me, he had lost sixteen pounds in weight. Because of his obstructive symptoms it was thought



Fig. 1. The resected specimen of ileum with its accompanying mesentery and glands is shown.

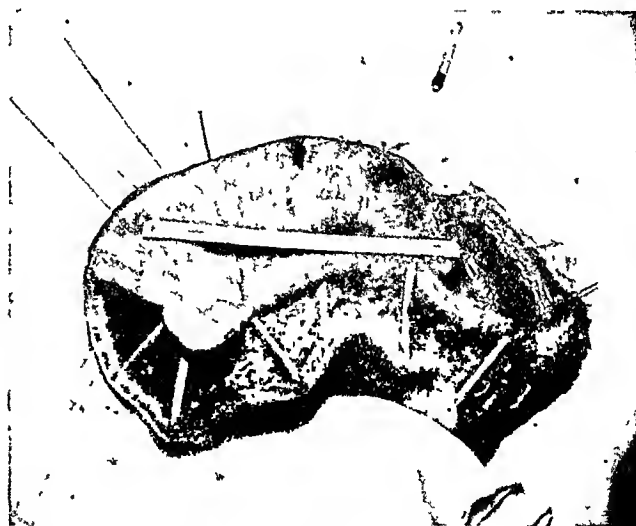


Fig. 2. The opened bowel shows a very thickened, rubbery wall with extensive ulceration.

the process localized definitely before exploration. This has been possible due to the fact that the condition was thought of and an x-ray of the small bowel carried out.

Case Report: The patient was a white male, age 62, Caucasian, City Fireman. He first began having symptoms in 1942, which symptoms consisted of severe lower abdominal colicky pain associated with some distension and some nausea but no vomiting. There had been no change in the stool findings. There had never been any bleeding, and there had been no diarrhea.

that, at his age, he might have a new growth in his colon. Proctoscopic examination was entirely negative for 25 centimeters. An x-ray of his colon revealed multiple diverticula of the sigmoid colon, but without any evidence of obstruction or inflammation, although it had been presumed previously that the diverticula had caused trouble and certainly this was a definite possibility. The question arose as to whether he might not have some adherence of the sigmoid to the bladder due to the fact that he had had some attacks of urinary tract infection, however, the pylorograms and cystogram

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were entirely negative. There was no evidence of any internal fistula. An x-ray of the small bowel revealed an obstructive lesion involving the lower ileum. The lower six inches of the ileum was normal. The pre-operative diagnosis therefore was made of regional enteritis, involving the ileum, the lower six inches of the ileum being entirely negative.

Exploration was carried out on February 15th, 1943, at which time the entire colon was explored and found to be negative except for multiple diverticula without evidence of inflammation. There were no adhesions. The omentum was free. The ileum was involved for a distance of about twenty four inches, the ileum being very markedly thickened and indurated. The accompanying mesentery glands were quite markedly swollen. The lower six inches of the ileum was not involved. The cecum was quite normal. Examination of the remaining portion of the small intestine revealed no other area of enteritis. About twenty-four inches of the ileum was removed, together with its mesentery glands. The terminal ileum was inverted and the proximal ileum was anastomosed to the transverse colon by an end to side ileocolostomy. The patient was given 500 CC's of citrated blood. His immediate and subsequent post-operative course was quite uneventful. Nasal

suction was instituted for the first five days. After that he was allowed to take his fluids by mouth. Pathological examination revealed an ulcerative enteritis of the ileum, the bowel wall being quite thickened. There was no evidence of any tuberculosis. The patient was allowed to leave the hospital on the tenth post-operative day and progressively and rapidly improved. He was able to return to his duties as a city fireman within six weeks and within three months had gained twenty pounds in weight. His bowels were working normally and a check-up x-ray revealed that his ileo-colostomy was functioning quite normally. His condition has continued to remain quite well.

COMMENT

We ordinarily look upon a condition of regional enteritis being a condition occurring in young individuals. It is more common in the male sex. The terminal ileum is involved in the majority of cases but any part of the intestinal tract can be involved. Cases of involvement of the terminal ileum and cecum are now being reported. Also multiple areas of involvement are not uncommon. It is common enough so that multiple areas should always be looked for. I feel that primary resection should be carried out whenever advisable.

Book Reviews

Review on an "Encyclopedia of Endocrinology" Section I "The Steroids". By Hans Selye, McGill University, Montreal, Canada. Published in 4 volumes by A. W. T. Franks, Publishing Company, Montreal, 1943.

This is the first section of an Encyclopedia which it is proposed will encompass the entire field of endocrinology. As such it will be the first handbook on this subject published in the English language. Because endocrinology has such a wide scope this work should be of unusual interest not only to students of endocrine research but to all those interested in medical sciences in general. The author is well qualified to prepare such a work as he has wide experience in many aspects of experimental endocrinology. To facilitate the preparation of this handbook the author has collected over 150,000 reprints and abstracts on endocrine topics.

The present section, which is the first to appear, is a "Classified Index of the Steroid Hormones and Related Compounds." It is published in four attractive loose leaf binders. The choice of the loose leaf system is particularly suited for this section as it permits the addition of new sheets as further information becomes available and new compounds are prepared, and allows the rearrangement of the index to suit the individual needs of the reader.

The system of classification used in this index is based on chemical structure. It lists all the steroids as substitution products of saturated nuclear hydrocarbons. These are norestrane, estrane, D-homoestrane, pyroandrosterane, 18-norandrosterane, i-androsterane, androsterane, D-homoandrosterane, etiocholane, 9-epietiocholane.

By this method of classification pregnane, for example, becomes an alkyl substituted derivative of etiocholane. A separate page is devoted to each parent compound. In all 728 compounds are indexed. Each index page consists of the name of the compound, assigned according to the above classification, with the common name if such exists in parenthesis. Seven section headings appear on each page. They are: Isolation, Structure and Synthesis, Melting Point, Pharmacology, Remarks, Derivatives and References. Under each heading the information at present available concerning the compound is recorded and the requisite literature references given.

The index thus presents information which can be obtained from the original publications only at great trouble with a considerable expenditure of time. The last such exhaustive classification appeared in "The Chemistry of the Steroids" by Dr. H. Sabotka of which no edition has appeared since 1938. It is of particular interest to pharmacologists and biochemists, but perhaps of less use to the organic chemist as the sterols, bile acids, etc., are not indexed.

This section of the Encyclopedia contains several extremely useful synoptic tables. Perhaps of greatest interest is the synoptic chart which summarizes all the information available regarding the hormonal activities of all the known biologically active steroids and their derivatives. This section alone makes the index an indispensable reference volume as many of the data herein recorded can be found in the original literature only with the utmost difficulty.

This section represents what must have been a long

and tedious task for the author and he is to be congratulated on the excellence and completeness of this work. The book is indispensable to any Laboratory in which the steroid hormones are studied, particularly since the author proposes to keep the index up to date by the periodic publication of supplementary sheets.

Lectures on the Kidney. By Homer W. Smith. Pp. 134 (\$1.00). University Extension Division, University of Kansas, Lawrence, Kansas, 1943.

This book presents three Porter Lectures delivered at the University of Kansas Medical School and two William Henry Welch Lectures at the Mount Sinai Hospital of New York. One cannot be familiar with renal physiology and the subject of renal clearance without knowing the important contributions made by Professor Smith and his co-workers. The history of the search for a method for studying renal clearance is told entertainingly in a lecture entitled "Renal physiology between two wars."

Other lectures include "The evolution of the kidney," "Newer methods of study of renal function in man," "The renal blood flow in normal subjects" and "Application of saturation methods to the study of glomerular and tubular function in the human kidney."

As one might expect, the lectures cover fundamental principles and point out the applied physiology. Emphasis on the human kidney and examples of renal pathology in man are numerous. The methods of measuring blood flow and filtration rate which were introduced into the physiological laboratory have paid enormous dividends when applied to the study of the human kidney. The physiologist and the clinician wishing authoritative information on problems of kidney function will find this book both interesting and instructive.

Dictionary of Bio-Chemistry and Related Subjects. Edited by William M. Malisoff. Pp. 579 (\$7.50). New York, Philosophical Library, Inc., 1943.

This dictionary is a combination of an alphabetical glossary of biochemical terms and an encyclopedia. To achieve this combination, fairly lengthy discussions of certain topics are interspersed with the more conventional brief definitions. The lengthier discussions, many written by authorities on their respective subjects, are by no means exhaustive but do offer sufficient information to orientate the reader. Cellulose decomposition by micro-organisms, cardio-active digitalis glycosides, glycosuria, insulin, plant-growth hormones and biological effects of radiation are a few of the items which have received greater attention.

The definitions of a number of terms are open to question. To define pH as "a direct measure of acidity or an indirect measure of alkalinity" is certainly not enlightening. Saliva is said to be "a secretion of the parotid glands containing an amylase (ptyalin) and a mucin" and no mention is made of the submaxillary and sublingual glands. Furthermore, the saliva of certain species (e.g., the dog) contains no amylase. The fundus is designated as the body of the stomach, a point which does not agree with standard texts on anatomy.

Several typographical errors are present. It is a pity that most of the graphs and tables are poorly reproduced. This fault distracts from the worth of the book. The numerous source references to periodical literature, many of them in European journals, are valuable.

As a pioneering effort, the dictionary is unique and will fill a definite need, particularly among doctors and science teachers. It is a worthwhile project and should prove valuable if some of the inconsistencies and the poor diagrams are corrected in future editions.

Borderlands of Psychiatry. By Stanley Cobb. Pp. 166 (\$2.50). Cambridge, Harvard University Press, 1943.

In the United States there are at present some 700,000 mentally disordered patients in institutions; of these about 600,000 are demented whilst the remainder are mentally defective or feeble. An estimated 3 to 5 million people exist in the community, outside institutions, who are either demented or amented but for one reason or another are not institutionalized. What Cobb calls the "borderland cases" make up the subject of this book. These cases are some 6 million people who suffer from a personal disorder of some type that requires medical attention. The medical man consulted often is the psychiatrist, but frequently too it is the neurologist and internist. Included among these borderland cases are those afflicted with stammering, epilepsy, some types of sexual perversions, chronic alcoholism, and "other neurological" conditions. These miscellaneous conditions are numerous and, as Dr. Cobb points out, the difficulty is not whom to include but whom to exclude. If all the emotional maladjustments are counted, then "all the world is queer but thee and me, and thee's a little queer."

This excellent book will appeal to the physician, whether he is in general practice or in a specialty. The author is professor of neuro-pathology at Harvard and also chief psychiatrist at the Massachusetts General Hospital. He thus approaches his problem from both the angle of the "functionalist" and the "structuralist." The discussions on structure and function in the past have been too biased, particularly where the etiology of mental disease is concerned. His conclusion, that every symptom is both functional and organic, is a step out of the dark. One passage from this excellent book is worth quoting, since it both reveals Dr. Cobb's views and serves as a sample of his style of writing:

"The difference between psychology and physiology is merely one of complexity. The simpler bodily processes are studied in physiological departments; the more complex ones that entail the highest levels of neural integration are studied in psychological departments. There is no biological significance to this division; it is simply an administrative affair, so that the university president will know what salary goes to which professor."

Biochemistry for Medical Students. By Wm. V. Thorpe. Third Edition. Pp. 476, (\$4.50). Baltimore, Williams and Wilkins Co., 1943.

This textbook was written to fulfill the needs of medical students studying biochemistry. It is rather

surprising how well the author has succeeded in condensing the subjects discussed without leaving the impression that only an outline is being presented. The text as a whole is written authoritatively and only a few statements may be open to question. Unlike some other textbooks, this does not sacrifice certain fundamentals (e.g., physical chemistry) for the sake of space to consider biochemical aspect of pathological conditions. Basic principles are well presented and the book should prove useful in most courses in biochemistry for medical students. It should also serve as a useful "refresher" for those physicians who are desirous of brushing

up their biochemistry but do not have time to read larger books.

The section on digestion is fairly good. One point, however, requires attention, namely the definitions of "choloretic" and "cholagogue." The author adheres to the British custom of defining cholagogue action as that which stimulates the secretion of bile. The more recent custom in American schools is to designate a cholagogue as a substance which causes the gall bladder to empty and a choloretic as one which stimulates the liver to secrete more bile. A minor point perhaps, but one which can be confusing to the medical student.

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M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

STEELE, G. H.: *Carcinoma of the oesophagus*. (*Lancet*, V. 2, P. 797, Dec. 25, 1943.)

This case is one of resection with anastomosis of a malignant ulcer partly in the esophagus and partly in the stomach of a 53-year old woman. Steele gives this as the first successful operation of its kind yet reported in England.

The diagnosis was arrived at by (a) history of progressive dysphagia of 3 months' duration, (b) X-ray finding of filling defect, and (c) esophagoscopy with biopsy. A gastrostomy and exploratory operation was followed in 15 days by the anastomosis operation. Under avertin, gas, and oxygen, the thorax was opened transversely at the 9th interspace from the costal margin to the transverse process dorsally. The diaphragm was split and the spleen removed; the coronary arteries ligated and the lesser-curvature glands stripped, and the esophagus separated with intact blood supply. The tumor was then removed, the gastric stump closed and the anastomotic incision made through the fundus, following the Ogilvie principle of the advantage of better fundal upward displacement. The suture line finally reached the level of the aorta.

Convalescence was complicated by a loculated empyema at the site of drainage. Gastrostomy tube was discarded in 10 days, and the patient was well five months postoperatively.

A relatively young patient and an operable growth, plus expert assistance, are listed as factors contributing largely to the success of the operation.—J. Garcia Oller.

STOMACH

WILEY, H. M.: *Fibroma of the stomach: case report*. (*J. Missouri M. A.*, V. 40, P. 171, June, 1943.)

Benign tumors of the stomach are infrequent and usually are asymptomatic, although they may often simulate a malignant lesion. Usually the gastric walls not including the curvatures are affected. The mucosa surrounding the lesion appears normal radiologically. Peristaltic disturbances and retention are infrequent. The case of a 51-year old male is presented; a previous diagnosis of gastric gumma was later changed to carcinoma; resection proved the lesion to be a fibroma.—D. A. Wocker.

GUYER, R. B.: *Comparison of radiological and gastroscopic findings in 200 dyspeptic soldiers*. (*Brit. J. Radiol.*, V. 16, P. 241, Aug., 1943.)

The 200 routine admissions for dyspepsia were all examined by X-ray and gastroscopy. Nearly all the patients had a history of dyspepsia in civil life. Clinical symptoms were vague epigastric distress or pain, relieved by vomiting, weakness, headaches. Radiological and gastroscopic examinations are not competitive but supplemental. X-ray showed the viscus as a whole whilst the gastroscopy revealed only the mucosal membrane, but in detail. Of the 200 patients, 73.5 per cent were normal radiologically, 47 per cent normal gastroscopically, and 40 per cent normal by both methods. Of those normal by X-ray, 30.5 per cent showed gastritis by gastroscopy. Duodenitis by X-ray and gastritis by gastroscopy were seen in 6.5 per cent of the patients.—F. E. St. George.

BOWEL

METHERY, D.: *Delusive calm following jejunal rupture by non-penetrating abdominal trauma.* (*Western J. Surg. Obstet. Gyn.*, V. 52, P. 34, Jan., 1944.)

Rupture of the jejunum by non-penetrating trauma of the abdomen is a relatively rare condition. Gross soiling and board-like rigidity may not occur until 12 to 24 hours after the rupture. The lesser symptoms, which occur during this quiet interval may be important in making proper diagnosis but unfortunately other injuries which sometimes are present confuse the picture.—D. A. Wocker.

HAWKSLEY, M.: *Hirschsprung's disease.* (*Proceed. Royal Soc. Med.*, V. 36, P. 586, Sept., 1943.)

Five cases of megacolon were selected from a series of 14 to demonstrate certain points in differential diagnosis of Hirschsprung's disease. In megacolon visible peristalsis and retention of barium enema are absent whilst these features are always present in Hirschsprung's disease. Treatment by spinal anesthesia has yielded good results. The improvement may be slow, usually about 4 weeks or longer. More than one spinal anesthesia may be required. Spinal anesthesia gives as good results as sympathectomy and no operative risk is encountered. A plea for its trial is made.—F. E. St. George.

LEMMCKE, P. A., QUINLIVAN, J. J. AND ORCHARD, N. G.: *Epidemic diarrhea of the new-born: a report of two outbreaks.* (*Am. J. Pub. Health*, V. 33, P. 1263, Oct., 1943.)

Two outbreaks of diarrhea of newborn infants occurred in a hospital in Rochester, N. Y., within a four month period. In the first outbreak the disease seemed to be transmitted chiefly by contaminated rubber nipples and formulae, and to a lesser extent by indirect contact; in the second it was apparently transmitted by faulty maternal breast technic. Both outbreaks promptly came to an end following control measures based upon studies of the mode of transmission.—George P. Blundell.

MACGREGOR, A. R. AND HENDERSON, J. J.: *Intestinal thrush.* (*Arch. Dis. Child.*, V. 18, P. 186, Dec., 1943.)

While the incidence of oral thrush in infants is fairly high, particularly among infants in nurseries and in those fed artificial diets, intestinal thrush, either primary or associated with oro-pharyngeal thrush, is rare. The infection from the mouth or oesophagus spreads to the stomach only in rare cases and to the intestine in only a very few instances. The thrush fungus, *Monilia albicans*, appears to be destroyed when it enters the blood stream but lesions of the brain, lungs, kidneys, joints and bones show that destruction is not always accomplished.

The authors present two cases, both in infants under two months at the time of death. One infant showed extensive ulceration of the superficial mucosa with encroachment of the inner muscularis but no penetration. The other infant showed an ulcer of the ileum which

penetrated through the muscularis to the subserous coat.—N. M. Short.

BAIRD, L. W.: *Roentgenologic diagnosis of carcinoma of the colon.* (*Texas State J. Med.*, V. 39, P. 243, August, 1943.)

In the colon, carcinoma is the tumor most frequently observed. It is being diagnosed at present in earlier stages than it was in the past. Barium meal is unsatisfactory, particularly if an obstruction is present. The barium meal should be used only after a contrast enema. Carcinoma in barium enema studies is indicated by an abrupt change in the mucosal pattern. Diagnosis becomes difficult when complications of obstruction or perforation are present. Complete obstruction is more commonly found in the left colon. Overdistension of the distal colon with barium, air or both, reveal two convex spurs on both sides of the obstruction: the author believes this is pathognomonic of carcinoma. Of 100 consecutive tumefactive lesions seen roentgenologically, 86 were primary carcinomas.—F. N. Chockley.

HURST, ARTHUR: *Discussion on functional diseases of the colon and rectum.* (*Proceed. Royal Soc. Med.*, V. 36, P. 639, Oct., 1943.)

A brief review of the normal physiology of the colon and rectum precedes a discussion of various functional disorders. Constipation may be either colonic constipation, in which the passage through the colon is delayed, or dyschezia, in which the feces pass through the colon in normal time but final evacuation is delayed owing to inefficient defecation. Dyschezia may be due to impaired conditioned reflexes for defecation or to failure of the final unconditioned defecation reflex. Impaction and dilatation of the rectum eventually leads to loss of sensation of distension; voluntary defecation is still possible but the patient usually believes that he must take an aperient to "get his bowels opened."

The presence of mucus in the stool is a normal event since the mucus is secreted by the colon as a lubricant. Colonic irrigation in some American "colon laundries" is decried by Hurst because it is an unnatural mechanical irritant resulting in damage to the mucus membrane. He regards mucous colitis as a mythical malady.

Paroxysmal proctalgia or proctalgia fugax is commonest amongst doctors. The pain is always purely perineal and does not radiate. The patient becomes pale, cold, breathless and may lose consciousness. An aura may be present. The pain is generally nocturnal. It may follow within a few minutes of normal coitus, especially its resumption after abstention, coitus interruptus or masturbation. Inflation of the rectum with air may bring relief. The etiology is unknown; the stools and bowel functions are normal.—F. E. St. George.

LIVER AND GALL BLADDER

PORTIS, SIDNEY M.: *The recognition of incipient liver disease.* (*J. Mount Sinai Hospital, New York*, V. 10, P. 152, May-June, 1943.)

Criteria for the diagnosis of liver disease before outstanding symptoms show themselves are given. An etiologic factor may frequently be found by careful interrogation of the patient. Some of the responsible factors are alcohol, deficient vitamin B complex intake, dietary restrictions (for reducing weight, etc.), gall-bladder disease, industrial poisons, malaria, syphilis. Whether all these conditions or factors are causative or only co-existing is not clear. No one liver function test is satisfactory. Tests differentiating normal from abnormal liver functions are adequate only when liver damage in early stages can be revealed. Among the recommended tests are included the intravenous hipuric acid test, cholesterol-cholesterol ester ratio, intravenous double glucose tolerance test, bilirubin metabolism test, and the colloidal gold and cephalin-cholesterol flocculation tests.—D. A. Wocker.

BACON, R. D.: *The fat meal—its value in cholecystography.* (*Penn. Med. J.*, V. 47, P. 137, Nov., 1943.)

The absorptive and concentrating function of the gall-bladder has received much attention but the function of contractility has been neglected. Gall-bladder disease has been proven many times by failure of the bladder to exhibit proper emptying although other cholecystographic features were normal. Perhaps as many as 5 per cent of all cholecystographies exhibit poor emptying as a single variation from the usual normal response. The fat meal phase of the cholecystographic study should be done as the early part of the test, and should be repeated if necessary. Twelve cases which came to surgery are presented. All exhibited adequate dye-concentrating ability but poor emptying in response to a fat meal. Organic wall disease was found present in eleven of the cases; the twelfth had preobstructive carcinoma of the distal colon and the poor gall-bladder contractility probably was due to reflexes from the colon.—Wm. D. Reamer.

NONNENBRUCH, W.: *Prognosis of hepatic cirrhosis.* (*Deutsch. med. Wochenschr.*, V. 67, P. 1055, 1941.)

The prognosis of an individual case of liver cirrhosis is difficult to determine. A compensated cirrhosis may remain symptom-free for years, only to become decompensated on a slight intercurrent stimulus. Severe cirrhosis may become compensated. Diagnostic tests are of little value in establishing prognosis.—Biological Abstract.

THOMAE, ROLF: *Traumatic parenchymatous atrophy of the liver.* (*Deutsch. med. Wochenschr.*, V. 67, P. 903, 1941.)

A case of fatal trauma to the liver parenchyma in a 47-year old female is presented and compared with six other reports in the literature of acute or subacute hepatic atrophy following physical injury.—Biological Abstract.

ULCER

CONNELL, F. G.: *Partial fundusctomy (proximal gastrectomy).* (*Ann. Surg.* 118, 1000, Dec., 1943.)

The author reports a 10-year follow-up on a patient

operated upon at the age of 24 for intractable duodenal ulcer. The patient had had a perforating duodenal ulcer in May, 1928 and a gastro-enterostomy complicated by jejunal ulcer. The gastro-enterostomy was subsequently taken down. In December, 1931 he had a partial gastric fundusctomy (proximal gastrectomy) performed. In January, 1932 one month after operation, test meal showed free hydrochloric acid 0, total acid 37. In November, 1934 the free hydrochloric acid was 37, in September, 1941 free hydrochloric acid 20. Unfortunately there is no record of the gastric acidity before the fundusctomy. The patient has remained well without complaints for 10 years.

A review of the records of 25 cases in which a similar operation has been done is then presented. In 19 cases the results were clinically satisfactory. Normal gastric function was found to occur by various authors mentioned. All cases were definitely intractable and each was very complicated. The appendix had been previously removed in 18; gastro-enterostomy had been performed in nine cases; cholecystostomy in one; taking down of a gastro-enterostomy in three cases; acute perforation had been closed once in eight cases and twice in three cases; acute massive hematemesis had occurred in three cases; combined jejunal and duodenal ulcers in one case; "kissing" duodenal ulcer in one case and gastrojejunal fistula in two cases.

Under these unfavorable circumstances the results are definitely encouraging and apparently interfere less with normal gastric function than the present accepted distal gastrectomy, which is based on the unproven Edkin's theory. The report was made with the aim of encouraging others to give this method a clinical trial in intractable cases of duodenal ulcer. An excellent bibliography is appended.—Adolph A. Walkling.

MAILER, R.: *Perforated peptic ulcer.* (*Lancet*, V. 246, No. 6282, P. 133, January 22, 1944.)

About 30 per cent of an unstated number of patients operated on for perforated peptic ulcer had no symptoms; 70 per cent had recurrence of symptoms after perforation and in 40 per cent the symptoms were severe. Mailer believes the patient may be operated on too early just as easily as too late. He believes a delay of 2 to 3 hours is advisable to permit the patient to recover from shock. In the past 4 years he lost 3 out of 61 patients (less than 5 per cent) whereas in 1938, the author reported a loss of 11 per cent in 72 cases. Improved technique, experience, and sulfonilamide interperitoneally are reasons for the improvement. He believes that sulfonilamide is most helpful in late cases and that early use only interferes with fibroblastic responses. The duodenal ulcers outnumber the gastric by 10 or 12 to one.

GULZOW, M.: *Insulin shock therapy in ulcer.* (*Deutsch. med. Wochenschr.*, V. 67, P. 1115, 1941.)

Insulin shock has a beneficial effect upon gastric or duodenal ulcers despite the resultant hypersecretion and hyperacidity. Doubt is cast on the importance of hyperacidity in ulcer pathology. A strong hyperemia

of gastro-intestinal mucous membrane accompanies insulin shock, and the therapeutic effect on ulcers is considered due to this.—Courtesy Biological Abstracts.

EPPINGER, HANS: *Ulcer genesis and ulcer therapy. Also additional study of effects of vagotomy.* (Deutsch. med. Wochenschr., V. 67, P. 1111 and 1145, 1941.)

Vagotonia is discussed in respect to the view that chronic constipation and gastric and duodenal ulcers are not localized conditions but evidence of a systemic disorder. Causation of ulcers involves the activity of the gastric juice and the resistance of the tissue. In turn, capillary damage or vasospasm, damage to the mucous membranes either through ingested or hemato-genous noxious factors, and mechanical damage to the mucous membrane may play a role. The effects upon these factors of chronic constipation and its associated septicemia are discussed. High protein intake favors ulcer formation, while vegetable foods have a healing influence. Cellulose should be increased gradually in the diet and hypertonic glucose gastric lavage should be combined with this dietary treatment. Abstinence from tobacco and the removal of focal infections are helpful. Oral administration of larocaine solutions is useful in the early stages.—Biological Abstracts.

NORDMANN, O.: *The prognosis of surgical intervention in gastric and duodenal ulcer—addition to work of Kalk.* (Deutsch. med. Wochenschr., V. 67, P. 1121, 1941.)

Indications for gastric surgery are discussed together with a consideration of prognosis with different procedures.—Courtesy Biological Abstracts.

THERAPEUTICS

GLASER, K., AND BRUCE, J. W.: *Treatment of epidemic diarrhea and dysenteries in infants and young children.* (J. Pediat., V. 24, P. 53, Jan., 1944.)

The improvement of results in the treatment of diarrhea and dysentery over a period of two years are given. The patients were divided into two groups for this discussion: (1) diarrhea classified as nutritional and also those caused by parenteral infection; and, (2) dysenteries with "specific" illness caused by organisms belonging to the dysentery group. Except for the isolation technic observed in the dysentery form and the different selection of sulfonamides, the same method of treatment was applied in both conditions.

The main principles of the treatment were outlined as follows: (1) starvation period of 12 hours to provide rest for the irritated intestine; (2) oral and intravenous hydration and combatting of acidosis; (3) feeding of buttermilk, skimmed boiled milk, or protein milk in from 3 to 4 hourly intervals, the amount regulated entirely by the appetite of the patient, to provide adequate caloric intake; (4) sulfathiazole and sulfaguanidine; (5) plasma and blood transfusions; (6) specific antiserum therapy; and, (7) bismuth and papegoric only in treatment of the resistant patient.

This resulted in a decrease in (1) the average hos-

pitalization time, (2) the total number of deaths, and (3) the death rate.—George P. Blundell.

PAGE, S. G.: *Sulfaguanidine in the treatment of bacillary dysentery.* (Bulletin U. S. Army Med. Dept., No. 72, P. 50, Jan., 1944.)

Five hundred and twenty cases of acute bacillary dysentery were treated with sulfaguanidine at a station hospital in Northwest Africa during the 5 week period ending June 28, 1943. Bacteriological examinations, done under field conditions, showed 208 patients to have positive stools. *Shigella paradyentery* accounted for 91.4% of these positives and *Shigella sonnei* for 8.6%. After the initial admission-stool was obtained for culture, a routine ten-day course of sulfaguanidine was started. For this period the average total dosage was 130 grams. The response to this therapy was very rapid. Only 2.8% of the entire series of cases required a second course of sulfonamide (sulfadiazine) to render their stools negative. Only three cases of drug fever were seen. Control cases were observed. Three negative stool cultures were considered inadequate as proof of the noninfectivity of the patient, for the organism appeared intermittently in the stools of both treated and untreated patients. It was concluded that sulfaguanidine should be the drug of choice because of its effectiveness and low toxicity. The author regretted the fact that conditions did not permit the observation of these cases for any length of time.—George P. Blundell.

PIERINI, ALFREDO: *Acute intestinal obstruction—strangulation of the cardia; new therapeutic procedures. Preliminary report.* (Rev. Assoc. Med. Argentina, V. 57, P. 603, 1943.)

Intramesenteric injection of neostigmine is recommended both for therapy and diagnosis in acute intestinal obstruction. After relief of the obstruction, neostigmine causes rapid evacuation of the intestine; and the peristaltic response of the strangulated portion of intestine is an index of its viability.—Biological Abstracts.

SURGERY

RENTSCHLER, C. B.: *Aspects of gall-bladder surgery.* (Penn. Med. J., V. 47, P. 131, Nov., 1943.)

One thousand consecutive biliary tract operations at the Reading Hospital are reviewed. The best diagnosis is established by careful history and thorough physical examination. Elderly patients, or those with associated cardiovascular-renal lesions, do best with cholecystostomy alone. Proper preparation of the patient for surgery is important. Cardiovascular disease and malignancy accounted for the greatest number of post-operative deaths. Next in decreasing order of incidence of death were shock, acute hemorrhagic and suppurative pancreatitis, pneumonia and ileus. Bile peritonitis was responsible for only 3 deaths, ruptured gallbladder for 2 and liver insufficiency for 5.—Wm. D. Beamer.

BURNSFORD, J.: *Ulcerative colitis, treated by medication through a caecostomy.* (*Proceed. Royal Soc. Med.*, V. 37, P. 86, Jan., 1944.)

A 31-year old woman was admitted to hospital with acute colitis, dysenteric flux and exhaustion. Caecostomy was performed and a catheter inserted. Through this she was first treated with oxygen and later with cod liver oil. A generous diet, regardless of roughage, was maintained; hydrochloric acid was given with meals to counter-balance the acid-secreting deficiency usually present in these cases. Improvement was rapid.

This is one of a large series of colitis cases in which colonic medication was similarly given by appendicostomy.—F. E. St. George.

CONNER, G. J. AND HARVEY, S. C.: *Colostomy of the ascending colon or cecum.* (*Yale J. Biol. Med.*, V. 16, P. 261, January, 1944.)

The authors present a simplified procedure for formation of a colostomy which they believe eliminates several necessary or dangerous steps. The colostomy tends to close spontaneously, and closure is hastened by trimming back the mucosa to a level below that of the skin; no additional operation for closure is needed.—N. M. Short.

EXPERIMENTAL MEDICINE

SECRETION

MAJ, GIORGIO AND LUCIANO BONORA.: *Changes in the amylolytic function of the salivary glands following blockage of the external pancreatic secretion.* (*Pflugger's Arch. ges. Physiol.*, V. 246, P. 749, 1943.)

Ligation of the pancreatic ducts in dogs increased the amylolytic capacity of the saliva after about 20 days. This capacity remained high for a considerable time then slowly declined. Ligating only the duct of Wirsung was as effective as ligating all ducts. The diastatic capacity of the blood was not found altered in these experiments.—Courtesy Biological Abstracts.

ABSORPTION

ANDREWS, J. C. AND ANDERSON, C. E.: *The absorption of quinine sulfate and quinine dihydrochloride from isolated intestinal loops of dogs.* (*J. Pharmacol. Exp. Therap.*, V. 78, P. 346, Aug., 1943.)

The first pertinent factor in a study of the anti-malarial action of a substance is that of absorption. Using dogs with isolated jejunal loops, the authors found that quinine dihydrochloride is absorbed approximately five to six times as rapidly as quinine sulfate. (Incidental to the study was the finding that the solubility of quinine sulfate is increased in sodium chloride solution.) Even after experiments lasting 48 hours, 75 per cent of the amount of quinine absorbed from the intestine, in terms of the quantity present in the blood and excreted in the urine, is unaccounted for; its site of storage is unknown.—F. X. Chockley.

EXCRETION

RAMMELKAMP, C. H. AND HELM, J. D., JR.: *Excretion of penicillin in bile.* (*Proceed. Soc. Exp. Biol. Med.*, V. 54, P. 31, October, 1943.)

Penicillin is not inactivated by bile, saliva, or succus entericus. Gastric juice inactivates the drug. At times the penicillin was more concentrated in the bile than in the blood serum. This suggests that the liver may concentrate penicillin. The degree of its concentration in the bile proved great enough to kill gram positive organisms, a fact which may prove useful in treatment of infections of the biliary tract.

Five patients with normal functioning gall-bladders and one patient recovering from a cholecystectomy were given penicillin intravenously and observed. Of interest was the fact that in each of the patients with normal gall-bladders the concentration of penicillin in the bile reached its maximum at different times and in all five the concentration decreased irregularly. In contrast, in the patient without a gall-bladder, the concentration reached its maximum height in 15 minutes and then decreased gradually. The suggested explanation is that in the normal patients the intermittent emptying of the gall-bladder diluted the bile in the common duct.—R. L. Burdick.

PATHOLOGICAL CHEMISTRY

DRILL, V. A., ANNERGENS, J. H. AND IVY, A. C.: *Effect of cholecystectomy on liver function.* (*Prod. Soc. Exp. Biol. Med.*, V. 54, P. 242, Nov., 1943.)

The cholecystectomized animal or man remains in apparent good health although dilatation of the biliary ducts and hepatitis may occur. The present study was carried out on twelve cholecystectomized dogs. In ten dogs there was found a definite rise in serum phosphates. The high serum phosphatase level was maintained in nine of the animals and returned to normal in only one. Only four of these ten dogs developed an increased retention of bromsulphalein. It would appear that serum phosphates is a more sensitive index of the slight biliary obstruction than the bromsulphalein test. The mechanism by which the increased intraductal pressure, resulting from removal of the bladder, raises the serum phosphatase is unknown.—M. H. F. Friedman.

METABOLISM AND NUTRITION

ANDERSON, C. E., CORNATZER, W. E., AND ANDREWS, J. C.: *The role of the liver in the metabolic destruction of quinine.* (*J. Pharmacol. Exp. Therap.*, V. 79, P. 62, Sept., 1943.)

By removal of one-third to one-half of the liver of rats or by damaging the liver of a dog with chloroform, the amount of quinine excreted in the urine is increased. The urinary quinine returns to normal levels when the liver regenerates or returns to normal condition. These results indicate that the liver is the site of metabolic destruction of quinine and the authors believe that some special agent in the liver is responsible.—D. A. Wocker.

A Quantitative Study of the Inhibitory Effect of Acid in the Intestine on Gastric Secretion *

By

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PHILADELPHIA

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INTRODUCTION

About forty years ago Sokolov, (12) working in Pavlov's laboratory, observed that the introduction of 0.5 per cent HCl into the duodenum of a Pavlov-pouch dog inhibited the secretion from the pouch. Since then several workers have studied this problem but with discordant results. While some have reported that introduction of acid into the duodenum will stimulate gastric secretion (dog, man, 6, 7) others have reported inhibition (dog, 4) (man, 5, 11) or no effect (man, 13).

In a preliminary communication (8a and b) we reported what appeared to be a clue to the discrepancy in the reported results. It was observed that introduction of acid into the duodenum would inhibit the gastric secretion from a Pavlov pouch provided a threshold level of duodenal pH was attained. A reduction in volume of secretion of about 50 per cent was observed when the pH of the intestinal contents was about 2.5, while almost complete inhibition occurred when the pH was suppressed to 2.0 or lower. These observations were made on Pavlov-pouch dogs secreting in response to a test meal. The experiments reported in the present paper were performed to determine more fully the role of intestinal pH on the course of gastric secretion and to study some of the factors involved. In the preliminary communication we called attention to an apparent "rebound" or after-effect of increased gastric secretion following the inhibition. This phenomenon is being investigated in more detail and the results will be reported later.

METHODS

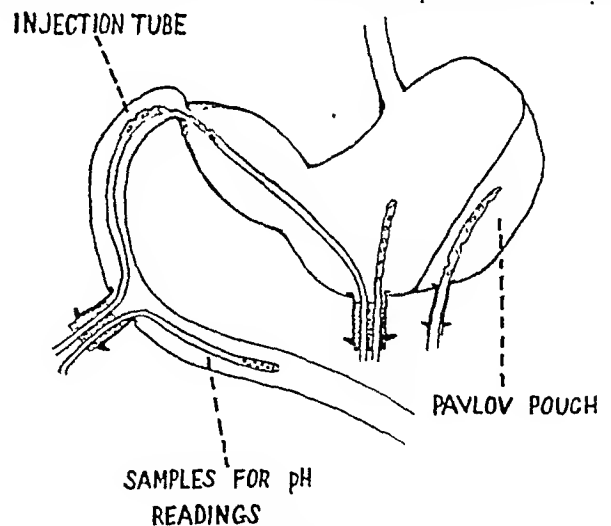
EXPERIMENTS were performed on three dogs equipped with a Pavlov pouch of the stomach and on one dog with a Heidenhain pouch. The Pavlov pouches were prepared by a previously described technic (17) which insures minimal interruption of the vagal supply to the pouch. Each of the four dogs was also provided with a gastric cannula and a duodenal cannula of a type described elsewhere. (16)

The standard diet fed to the animals consisted of ground beef, ground Purina dog chow, bread and milk. A supplement of 0.1 N HCl was added approximately equivalent to the amount lost daily by way of the pouch. The animals maintained their weight and remained in

good health on this regimen.

Experiments were begun in the morning, eighteen to twenty-four hours after the last meal, and carried through only when a long control period revealed that the stomach was in a fasting state. Various means were used to stimulate the secretion of gastric juice; these will be described in connection with the experimental results.

To study the influence of acid in the intestine the acid was introduced at a constant rate into the duodenum by means of a rubber tube passed through the duodenal cannula. In most of the experiments the acid



was introduced into the bulb of the duodenum (fig. 1). However, to check against the possibility that the results were due to reflux of acid from the bulb into the stomach, four experiments were performed in which the acid was introduced into the intestine at a distance of 12 to 15 cm. below the bulb, but no difference in results was observed. On rare occasions the instillation of acid resulted in the appearance of blood in the gastric or intestinal contents; all such experiments were discarded.

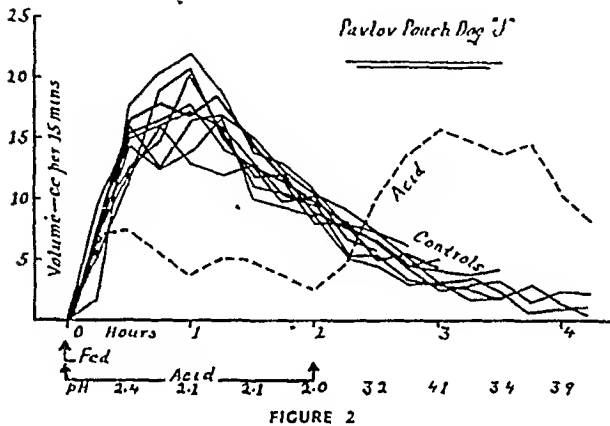
Samples of duodenal content for pH determinations were taken at thirty-minute intervals from a point approximately 12 to 15 cm. distal to the entrance of the acid. The pH determinations were made electrometrically, using a glass electrode. Free and total acidities of the gastric juice were determined in the usual manner, titrating with 0.01 N NaOH to Topfer's and phenolphthalein end points.

* Aided by a grant from John Wyeth & Brother, Inc.
** Ross V. Patterson Fellow in Physiology and Gastroenterology.
Submitted Jan. 17, 1944.

RESULTS

Gastric secretion in fasting dog. In the Pavlov-pouch dogs, fasting eighteen to twenty-four hours, the secretion from the pouch was scant, usually less than 3.0 cc. per hour. The acidity was low (total acidity 50 m. eq./l. average) and the juice consisted mainly of mucus. Instillations of acid into the duodenum for periods of one to three hours (120 to 850 cc.) were without effect on the rate or acidity of the pouch secretion, although some increase in the total output of pepsin was noted. This effect on pepsin has since been reinvestigated more fully and will be discussed elsewhere.

Gastric secretion of nervous origin. (a) Test meal. The standard test meal consisted of 300 Gm. of beef heart free from visible fat. The beef heart was either ground or cut up into small squares before feeding. The results of over 100 control experiments on the 3



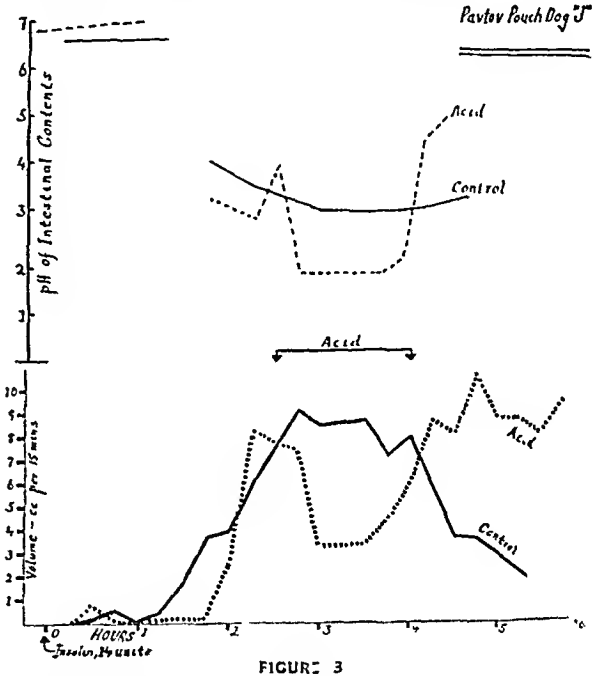
Pavlov-pouch dogs showed great constancy in the rate and acidity of the secretion from the pouch (fig. 2). The pH of the intestinal contents toward the end of the first hour following feeding usually ranged from 6.7 to 3.5.

In order to observe the effect of increasing the intestinal acidity the experiments were repeated with the addition of instilling acid into the duodenum immediately after the test meal had been fed. The acid was allowed to flow into the intestine for a period of time estimated to comprise the nervous phase of gastric secretion (one to two hours). The course of gastric secretion was found to be dependent on the pH of the intestinal contents. When the intestinal pH was about 3.0 or higher the rate of secretion was similar to that in the control experiments (table 1). When the intestinal pH was about 2.5 the secretion was depressed about 50 per cent as compared with the controls (table 1). Almost complete inhibition resulted when the intestinal pH was 2.0 or lower (fig. 2). In other experiments infusion of 0.9 per cent NaCl into the duodenum was without inhibitory effect (table 1).

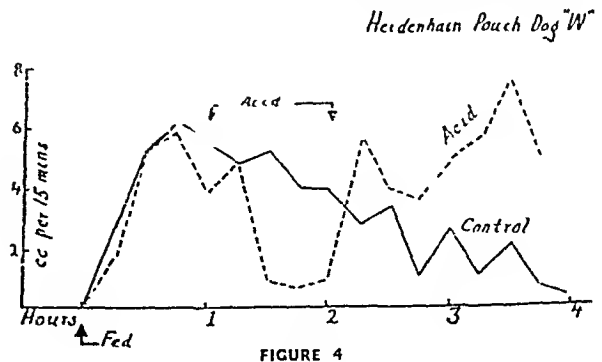
(b) Insulin. In each of six experiments 14 units of insulin were administered subcutaneously. In three of these acid was infused into the intestine during the secretory period that followed. It was found that a reduction in the volume of secretion of about 62 per cent occurred when the pH of the intestinal contents fell to about 2.0 (fig. 3).

Gastric secretion of chemical origin. (a) Test meal. The experiments on the Pavlov-pouch dogs were repeated as above on five occasions, except that the acid was infused into the intestine three to four hours after the feeding when the nervous excitation of the gastric glands was presumed to have subsided. Depression of secretion was obtained when the intestinal pH was about 2.5 or lower.

(b) Food placed in the stomach. In four experiments the 300 Gm. of ground beef was placed in the stomach of the Pavlov-pouch dog through the gastric fistula, with care to avoid exciting the animal or the establishment of conditioned reflexes. In two experiments the secretion which was thus provoked was inhibited by intraduodenal infusion of acid.



(c) Heidenhain pouch secretion. In seven experiments the standard test meal of beef heart was fed the Heidenhain-pouch dog, and in three experiments the acid was infused into the intestine either during the first, second or third hour following the feeding. In



inhibition of as much as 75 per cent was obtained when the pH of the intestinal contents was depressed to about 3.0 or lower (fig. 4).

Gastric secretion provoked by histamine. Several methods of stimulating the secretion of gastric juice by histamine were employed; the one found most practical in our study was as follows: Twenty minutes after an initial subcutaneous injection of 1 mg. histamine, injections of 0.3 mg. histamine were repeated every ten minutes for the duration of the experiment. The gastric juice was secreted at a rate which was approximately the same in each of the five experiments in which this standard procedure was adopted. In seven

into the intestine. With simple drainage of the contents of the main stomach to the outside it will be noted from table 2 that (1) although the intestinal pH was not depressed the pouch secretion was *less* and not more than when the stomach was not drained; (2) when acid was instilled into the intestine during drainage of the stomach the pouch secretion tended to return to the same level as in simple histamine experiments without the gastric drainage. The decreased pouch secretion on simple gastric drainage was, we

TABLE I
Effect of Instilling Acid or Saline into Small Intestine on Gastric Secretion in Response to a Standard Meal—Dog "B"

Procedure	HOURS											
	1			2			3			4		
	Vol.		Total acid	Vol.		Total acid	Vol.		Total acid	Vol.		Total acid
	Concen- tration	Out put		Concen- tration	Out put		Concen- tration	Out put		Concen- tration	Out put	
Control—standard meal only (11 experiments)	cc	meq/l.	mg.	cc	meq/l.	mg.	cc	meq/l.	mg.	cc	meq/l.	mg.
	63.4	133.2	291.89	67.2	151.9	372.59	48.9	154.4	276.00	33.8	154.1	190.20
Standard meal followed by infusion of 740 cc 0.15 N HCl into intestine for two hours (4 experiments)												
	42	99.8	38	53	96.9	53	74	109	84.5	150	110.6	166
Standard meal followed by infusion of 540 cc 0.9 per cent NaCl into intestine for two hours (4 experiments)												
	92	98.5	90.2	110	102.6	113	129	106.8	137.4	154	103	177.

other histamine experiments intraduodenal instillation of acid did not affect the volume or the acidity of the secretion from the pouch, even though the pH of the intestinal contents was depressed to 2.0 and lower.

Since in the control experiments the intestinal pH was already below 2.0, due to the entrance into the in-

think, due to loss of chloride and fluid from the body and when these were restored by intestinal administration of acid the pouch secretion returned to control levels. From our experiments it would appear that the pH of the intestinal contents has no influence on gastric secretion due to histamine.

TABLE II
Effect of Instilling Acid into Intestine on Gastric Secretion Provoked by Histamine—Dog "J"

Procedure	HOURS											
	1			2			3			4		
	Vol.		Total acid	Vol.		Total acid	Vol.		Total acid	Vol.		Total acid
	Concen- tration	Out put		Concen- tration	Out put		Concen- tration	Out put		Concen- tration	Out put	
	cc	meq/l.	mg.	cc	meq/l.	mg.	cc	meq/l.	mg.	cc	meq/l.	mg.
Stomach cannula closed	26.8	157	153.6	26.2	168	160.7	24.4	163	145.2	20.0	162	118.3
Stomach cannula open and gastric contents draining to exterior	25.6	162	151.4	24.6	170	152.6	14.6	159	84.7	4.6	143	24.0
Stomach cannula open and gastric contents draining to exterior. During third hour cc 0.1 N HCl was instilled into intestine	23.0	164	136.7	26.5	170	164.4	19.4	166	117.5	25.6	168	157.0

testine of the highly acid gastric contents from the main stomach, it was considered possible that the secretion from the pouch would have been greater in the control experiments if the acid contents of the main stomach had not entered the intestine. Six experiments were performed as outlined previously, but the contents of the main stomach were drained through the gastric fistula. When this procedure was used the pH of the intestinal contents usually stayed above 4.5 and was promptly depressed below 2.0 if acid was instilled

DISCUSSION

1. Our experimental results point to the existence of a mechanism for the autoregulation of the gastric secretion which is brought into play when the acidity of the intestinal contents reaches levels which may be harmful to the intestinal mucosa. The role of such a mechanism during the secretory period following a meal may be on certain occasions of considerable importance. During the digestion of a meat meal by the dog the acidity of the duodenum near the pylorus is gen-

erally near pH 4 while the content of the antrum of the stomach has a reaction between pH 2.0 and 3.0 (15). The existence of a threshold level of intestinal pH for inhibition of gastric secretion which our studies show to be within the pH range of the antral contents is suggestive. One of us (15) has suggested that the "receptive relaxation" of the duodenum which occurs when the stomach empties itself results in the accumulation of duodenal contents in the vicinity of the pylorus. Occurring at the moment of exit of the acid gastric contents, this would facilitate quick dilution and partial neutralization of the chyme (to about pH 4.0). We may now suppose that should this neutralizing ability of the duodenal contents be ineffective, then a second mechanism may be set into action, one which arrests the secretion of the acid at its source.

2. The intestinal phase of digestion is believed to give rise to a corresponding intestinal phase of gastric secretion (1). This phase of secretion is ordinarily not copious but may assume significant proportions if the gastric juice is prevented from entering the intestine (4). While such a secretion may prove of assistance for the digestion of food within the stomach, it would appear to be superfluous in the later stages when the stomach is empty and digestion is entirely intestinal. The suggestion has been advanced that the intestinal phase of gastric secretion is normally regulated to some extent by the acidity of the intestinal contents (4, 5, 11). Our results appear to cast some doubt on the validity of this assumption. In the dog, at least, little if any inhibition of acid secretion occurs if the intestinal pH is above a threshold of about 2.5. Acidities as great as this are rarely found in the dog's intestine following a test meal (2, 14, 15, 18). We are inclined to regard this mechanism as one which is set into action only during emergencies when other means of reducing the acidity of the intestinal contents have failed. The possibility, of course, remains that in man the threshold is at a higher level than pH 2.5, which would explain the results of Griffiths (5) and Shay et al. (11) who, with few exceptions (11), used less concentrated solutions of acid.

3. In these experiments we have attempted to study the factors involved in the inhibition of gastric secre-

tion by a high acidity of the intestinal contents. That mere distention of the intestine by the fluid is responsible is ruled out by the experiments in which large volumes of acid introduced into the intestine failed to result in inhibition when the intestinal acidity was below threshold level. A reflex involving the intramural plexus of the intestine and stomach alone appears unlikely from the experiments of Day and Webster (4). By instilling acid into the intestine these workers inhibited gastric secretion in a dog with the stomach completely separated from the duodenum. Furthermore, we obtained inhibition of secretion from a pouch which was separated completely from the main stomach and the intestine. Although gastric secretion stimulated through the parasympathetic nervous system (insulin and the nervous phase of secretion in the Pavlov-pouch dogs) was readily inhibited by acid, the parasympathetic nervous system is not necessarily involved in the inhibitory process. Inhibition of the secretion provoked by placing food directly into the stomach of the Pavlov-pouch dog and inhibition of secretion of the Heidenhain pouch support this view.

4. It has been reported that histamine-stimulated secretion is not as readily inhibited as food- or insulin-stimulated secretion when oils, (9) fat (10) or concentrated solutions of dextrose (3) are introduced into the small intestine. In view of the possibility that the inhibition observed in our experiments may be due to enterogastrone, it is of interest that we found intestinal instillation of acid failed to inhibit gastric secretion provoked by histamine.

SUMMARY

Acid introduced into the small intestine of Pavlov-pouch dogs inhibits gastric secretion in response to a meal, providing an adequate degree of intestinal acidity is attained. Marked inhibition of secretion occurs if the pH of the intestinal contents is about 2.5 and almost complete depression when the pH is 2.0 or lower. This regulatory effect of intestinal acidity on gastric secretion is not present when the secretion is provoked by histamine. The role of this regulatory mechanism during the secretory period following a meal and the various factors which may be involved are discussed.

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The Therapeutic Use of the Amino Acid Histidine in Allergy and Shock— "Histidine as a Factor in Histamine Epinephrine Balance"

By

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NEW YORK, N. Y.

THE role of histamine in the causation of such a wide variety of physiological disturbances as that ranging from shock and inflammatory reactions to a diversity of allergic manifestations has left the impression that histamine is a physiological misfortune in the human economy.

This conception is primarily due to observations made on histamine imbalance rather than on histamine function. When histamine is injected intravenously, a chain of severe reactions is observed characterized by either an anaphylactic reaction or shock which may lead to death. This reaction is an extreme which is not much different from the intravenous injection of its opposite adrenalin which likewise will lead to shock and death.

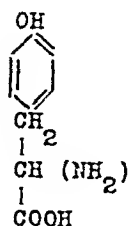
To view histamine as a toxin rather than a normal physiological agent of great value would be as incorrect as considering adrenalin a toxin even though in the broader sense we may consider it so in abnormal dosage. Once viewed from that angle, histamine adrenalin balance throws a new light on the study of shock, inflammation, allergies and smooth muscle tone.

While some schools of thought have attributed shock to the sympatho adrenal system, others have steadfastly held to the histamine theory of causation, yet the controlled balance of both mechanisms, one against the other, seems to have escaped observation. When histamine is inadequately opposed by adrenalin, there follows pronounced overaction of the histamine mechanisms such as occurs in sympatho-adrenalectomy.

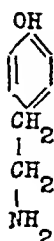
This is particularly evident during barbitol or ether anaesthesia. Histamine shock may appear. When overdosage of adrenalin occurs, the same picture results, so that neither the proponents of histamine as the cause of shock nor the believers in the sympatho-adrenal school can be considered as presenting the whole story. Dale and his associates produced fatal shock in etherized cats by injection of one or two milligrams of histamine, but unanaesthetized cats withstood ten times that dosage. Moon states that military surgeons reported that frequently a wounded soldier, whose condition was not critical, developed profound shock immediately when anaesthetized for operation. Sollman points out that etherization tends to lower the epinephrine store.

Two recent theories of shock have been considered diametrically opposed to each other. Selye explains shock as due to inadequacy of the physiological reactions, especially the adrenals, while Freeman proposes hyperactivity of the sympatho-adrenal system as the cause with anoxia resulting from prolonged maximal arterial constriction and evoked by pain, emotions or injury to tissues.

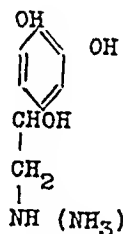
Neither of these theories take into consideration the biochemical and physiological relations of two balanced systems, histamine and adrenalin. These two substances have many parallel characteristics. Each has its origin in an amino acid, histamine from histidine and adrenalin from tyrosine through tyramine. A graphic illustration of epinephrine synthesis in vivo according to Schuler and co-workers is as follows:



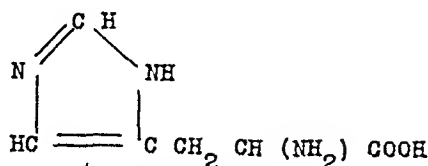
TYROSINE



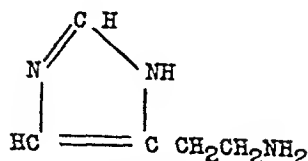
TYRAMINE



ADRENALIN



HISTIDINE



HISTAMINE

In both compounds decarboxylation of the amino acid leads to the final product, and a balanced relationship exists. Thus it has been shown that histidine goes to form histamine through decarboxylation in the presence of freely available carbon such as glucose and oxygen while adrenalin increases both blood sugar and oxygen. In this manner, the adrenalin response

TABLE 1. *Bronchiolar Response to Histamine Hydrochloride (Control Experiments)*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
Group 1					
Normal control					
		0	0	5.78	100.0
			2	5.61	97.0
			5	5.52	95.5
			8	5.62	97.2
			10	5.55	96.0
			13	5.50	95.1
			15	5.11	88.4
			17	4.92	85.1
			20	4.62	79.9
			22	4.51	78.0
			25	4.60	79.5
			27	4.23	73.1
			30	4.50	77.8
Histamine hydrochloride 1:50,000					
		0	0	5.60	100.0
			1	2.03	36.2
			2	1.68	30.0
			4	3.26	58.2
			6	3.76	67.1
			9	4.26	76.0
			12	4.52	80.7
			14	4.68	83.5
			17	4.71	84.1
			19	3.76	67.1
			22	2.63	47.5
			24	2.65	47.3
			27	2.90	51.7
			29	3.09	55.1

calls forth the biochemical antagonism of histamine. That this antagonism is mathematical, I have been able to show by testing the neutralization of histamine by adrenalin in the bronchiolar muscle of the rabbit. Here the bronchiolar constriction induced by histamine is

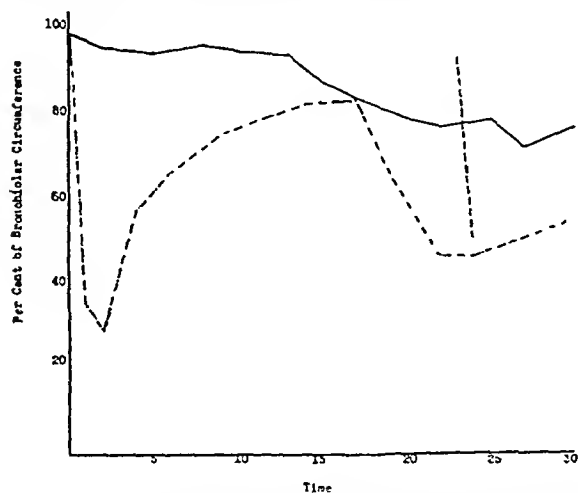


Chart 1 (group 1).—Effect of histamine hydrochloride on bronchiolar lumen. Experiment 1: Normal control (solid line). Experiment 2: Histamine control, zero minutes (line of dots and dashes); subsequent histamine control, twenty-four minutes (line of dashes). In this chart and in the accompanying charts, the number of minutes refers to the time at which the drug was added to the Ringer-Locke solution.

completely overcome by adrenalin chloride with a resultant dilatation of the bronchiole above normal.

The procedure followed the technique of Sollman and Gilbert, and with slight modifications of equipment,

proved practical. It affords such an excellent medium for the study of histamine that the procedure is here described in detail for future reference. In addition to demonstrating the direct neutralizing effect of adrenalin chloride on histamine, it was possible to demonstrate that the balance between histamine and adrenalin is influenced by other factors such as calcium and ascorbic acid. Calcium alone increased histamine constriction of the bronchioles. A similar result was obtained by Vanysek in 1914 with excised intestine as quoted by Sollman. This is interesting since we know that potassium salts increase epinephrine action by direct peripheral action through acetylcholine as shown by Hazard in 1933. Ascorbic acid had an antagonistic effect to histamine and diminished the bronchiolar constriction. Sodium ascorbate acted about the same as ascorbic acid. When however, the calcium was bound with ascorbic acid, the effect of the calcium was radically different leading to histamine antagonism greater than that of Vitamin C or sodium ascorbate. This again shows that physiologically, active agents work in systems which, when taken apart, can give erroneous impressions as to their activity in vivo. The ability of acetylcholine to increase adrenalin output is such a factor. Charts I to XII clearly show such relationships.

TABLE 2. *Antihistamine Action of Sodium Ascorbate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
Experiment 3					
Group 1					
Histamine hydrochloride 1:50,000					
		0	0	3.21	100.0
			2	0.59	18.3
			3	0.47	14.6
Sodium ascorbate 1:750					
		4	5	0.97	30.2
			7	1.00	31.1
			9	1.07	33.3
			12	1.57	48.9
			14	1.66	51.7
			17	1.71	53.2
			19	1.71	53.2
			22	1.72	53.5
			24	1.79	55.7
			26	1.77	55.1
			29	1.75	54.5
Experiment 4					
Histamine hydrochloride 1:50,000					
		0	0	2.92	100.0
			1	1.41	48.2
			3	1.18	40.4
Sodium ascorbate 1:750					
		4	5	1.38	47.2
			8	1.67	57.1
			11	1.78	60.9
			13	1.67	64.0
Histamine hydrochloride 1:50,000					
		14	15	1.89	64.7
			19	1.92	65.7
			22	1.94	66.4
			24	2.04	68.7
			27	2.02	69.1
			29	2.09	71.5

METHOD OF INVESTIGATION

For the purpose of this study the vitamin C salts of the aforementioned compounds were compared with the commonly used preparations. In this manner a most interesting synergistic action was revealed for all four preparations.

The object of the experiment was to secure a viable section of bronchiole. This was accomplished by fixing the lung of the rabbit in gelatin, chilling it and then cutting a thin section of a bronchiole, which was kept

in Ringer-Locke dextrose solution. The section was mounted on a ring so that when the gelatin was dissolved out the reactions of the bronchiole could be

neck muscles. The trachea was cut and a cannula inserted, which was held in place with hemostats. The lungs were filled to approximately normal expansion

TABLE 3. *Antihistamine Effect of Vitamin C (Ascorbic Acid)*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 5</i>					
Group 1					
Histamine hydrochloride	1:50,000	5	0	5.35	100.0
			6	3.23	60.3
			8	3.46	64.6
Vitamin C	1:750	9	10	3.77	70.4
			15	4.31	80.5
			18	4.34	81.1
			20	4.40	82.2
			23	4.37	81.6
			25	4.39	82.0
			28	4.44	82.9
			30	4.25	79.4
<i>Experiment 6</i>					
Histamine hydrochloride	1:50,000	1	0	3.75	100.0
			2	1.23	32.8
			3	1.05	28.0
Vitamin C	1:750	5	7	1.31	34.9
			9	1.66	44.2
			12	2.08	55.4
Histamine hydrochloride	1:50,000	16	15	2.05	54.6
			17	1.75	46.6
			18	2.17	57.8
			22	2.10	56.0
			25	2.05	54.6
			27	2.04	54.4
			30	2.06	54.9

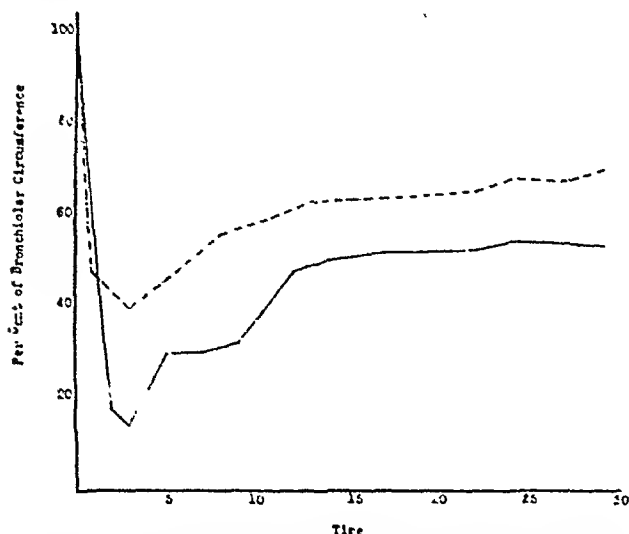


Chart 2 (group 1).—Histamine-antagonistic properties of sodium ascorbate. Experiment 3: Histamine hydrochloride, zero minutes; sodium ascorbate, four minutes (solid line). Experiment 4: Histamine hydrochloride, zero minutes; sodium ascorbate, four minutes; histamine hydrochloride, fourteen minutes (line of dots and dashes).

observed under the microscope and drawn to size. The whole procedure was conducted with adequate controls to assure the viability of the bronchiolar sections.

I first observed the technic of the microscopic study of bronchiolar reactions in the laboratory of Dr. H. D. Pease, who had constructed an ingenious microscope platform that permitted maintenance of a water bath of constant temperature for the ordinary Petri dish. This could readily be elaborated for a series of microscopes. In general, the technic of Sollmann and Gilbert was used as follows: Each of the following substances was dissolved separately in 500 cc. of water:

	Gm.
Sodium chloride	31.5
Potassium chloride	1.47
Calcium chloride	0.84
Sodium bicarbonate (NaHCO ₃)	1.15

The solutions were mixed and diluted to 3.5 liters. On the day of use, dextrose, 1 Gm. per liter, was added. Substances to be tested which are sufficiently soluble that a dilution of 1 : 50 is adequate are made up in distilled water. Those which are less soluble are made up in Ringer-Locke solution.

The animal was killed by intravenous injection of air. The skin was removed from the ventral portion of the abdomen, the thorax and the neck. A midline incision was made from the middle of the abdomen to the diaphragm. Lateral incisions were made just posterior to the diaphragm toward the sides of the body.

The diaphragm was punctured on each side, allowing the lungs to collapse. The ventral thoracic wall was removed, longitudinal cuts being made along the sides of the thorax anterior to the first pair of ribs. Care was taken not to cut the large axillary veins. A hemostat should be used on any small vessels which are accidentally cut. The first rib and the episternum were carefully removed, carrying with them the ventral

with gelatin (approximately 15 cc. of warm 10 per cent gelatin dissolved in Ringer-Locke solution for each kilogram of body weight). The inferior vena cava was clamped with a hemostat, and the lungs, heart and trachea were removed and placed in ice-cold Ringer-Locke solution (approximately 150 cc.). The organs were placed in the freezing compartment of the refrigerator for one to one and a half hours.

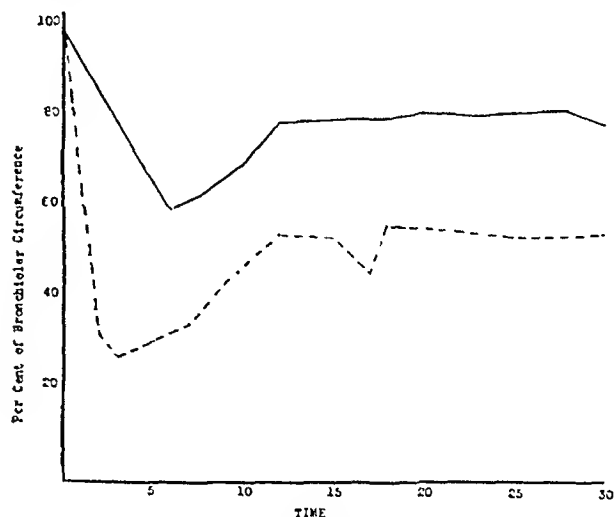


Chart 3 (group 1).—Histamine-antagonistic properties of vitamin C. Experiment 5: Histamine hydrochloride, five minutes; vitamin C (ascorbic acid), nine minutes (solid line). Experiment 6: Histamine hydrochloride, one minute; vitamin C, five minutes; histamine hydrochloride, sixteen minutes (line of dots and dashes).

The two large lobes of the lung were trimmed to approximately one-half size and thin sections of tissue cut across the bronchiole. These sections should be as

thin as possible (0.5 to 1 mm. in thickness). The sections were placed in the cold Ringer-Locke solution in which the lungs were kept. The sections were kept ice cold until each one was used.

TABLE 4. *Antihistaminic Effect of Ephedrine Sulfate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min)	Time of Observation (Min)	Area Arbitrary Units	Percent age of Original Area
<i>Experiment 3</i>					
Group 2			0	5.35	100.0
Histamine hydrochloride	1:50,000	2	3	2.72	50.8
			4	2.92	54.5
Ephedrine sulfate	1:10,000	5	5½	3.96	74.0
			7	3.86	72.1
			10	4.58	85.6
			13	4.66	87.1
			15	4.76	88.9
			18	4.85	90.6
			20	4.72	88.2
			23	4.77	89.1
			25	4.98	93.0
			28	4.58	85.4
			30	3.93	73.4
<i>Experiment 4</i>					
Histamine hydrochloride	1:50,000		0	5.21	100.0
		1	2	2.22	42.6
			3	2.50	47.9
Ephedrine sulfate	1:10,000	3½	4	3.08	59.1
			7	3.56	68.3
			10	4.01	76.9
			12	4.00	76.7
Histamine hydrochloride	1:50,000	13	14	4.08	78.3
			15	3.68	70.6
			17	3.71	71.2
			27	3.59	68.9
			30	3.47	66.6

If the substance to be treated was to be diluted, 49 cc. of Ringer-Locke solution was placed in the special dishes (9 cm. Petri dishes, in the center of which a ring of cork with a central opening, approximately 5

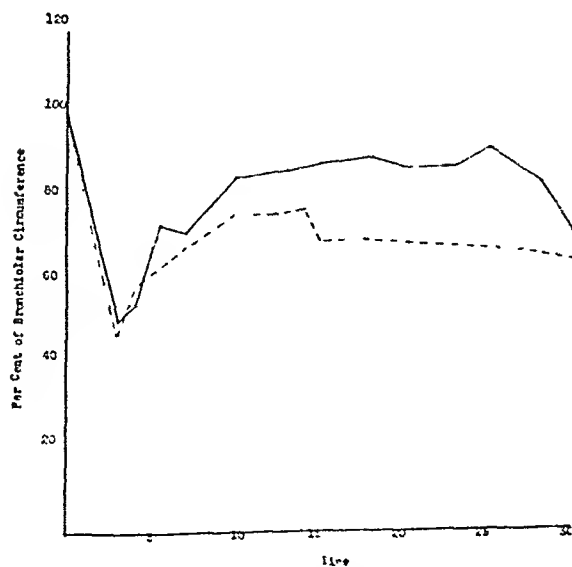


Chart 4 (group 2)—Histamine-antagonistic action of ephedrine sulfate. Experiment 3: Histamine hydrochloride, two minutes; ephedrine sulfate, five minutes (solid line). Experiment 4: Histamine hydrochloride, one minute; ephedrine sulfate, three and a half minutes; histamine hydrochloride, thirteen minutes (line of dots and dashes).

cm. in diameter, was cemented with beeswax). The section to be used was pinned out with the bronchiole over the opening of the cork. The sections should not

be stretched but should be pinned out flat. The dish was placed on the warm stage and the contents of the dish allowed to warm to 37 C., the section being agitated by means of a stream of Ringer-Locke solution from a small pipet. Camera lucida drawings of the bronchiolar lumen were made until it was of constant size (this usually took ten to fifteen minutes). The test solution was added near the edge of the Petri dish and mixed with the pipet. Then a small amount of fluid in the dish was picked up with the pipet and allowed to run out gently over the tissue. Camera lucida drawings were made as indicated by the reaction of the bronchiole.

In tests designed to show possible antagonism between two substances it was found that the second substance should generally be added about five minutes

TABLE 5. *Antihistaminic Effect of Ephedrine Ascorbate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min)	Time of Observation (Min)	Area Arbitrary Units	Percent age of Original Area
<i>Experiment 5</i>					
Group 2			0	2.67	100.0
Histamine hydrochloride	1:50,000	1	2	.52	19.4
Ephedrine ascorbate	1:10,000	3	4	1.67	62.5
			5	1.78	66.6
			8	1.60	69.9
			10	1.52	56.9
			13	1.43	53.5
			15	1.28	47.9
			18	1.31	49.0
			20	1.32	49.4
			22	1.27	47.5
			25	1.24	46.4
			28	1.17	43.8
			30	1.17	43.8
<i>Experiment 6</i>					
Histamine hydrochloride	1:50,000	1	2	0.57	100.0
Ephedrine ascorbate	1:10,000	3	4	1.75	26.6
			5	3.11	47.3
			8	4.16	63.3
			10	4.71	71.7
			13	4.84	73.6
			15	5.05	76.8
Histamine hydrochloride	1:50,000	14	15	4.70	71.5
			18	5.11	77.7
			20	4.73	71.9
			23	4.92	74.8
			25	5.06	77.0
			28	4.88	74.2
			30	5.00	76.1

after the first. The drawings made for each test were dated and a number assigned to each. Each drawing was labeled with the exact time of day, and later these times were translated into terms of minutes which elapsed after the section was put into the dish. These drawings were filed as a permanent record.

COMPUTATION OF RESULTS—The area of the bronchiolar lumen was measured in arbitrary units by means of a polar planimeter. The area just before the addition of the first substance to be tested was taken as 100 per cent, and was called the original area. Reactions were expressed as percentages of this original area which remained.

The animals used were white New Zealand rabbits, partially standardized as to age, weight, health and environment. Five animals were prepared and used as described.

The concentration of the solutions was kept equal

for all comparative tests. The solution of histamine was made up with 100 mg. of histamine hydrochloride to 100 cc. of Ringer-Locke solution. The dilution factor for all solutions of test substances was 1 : 50, giving with the histamine solution a 1 : 50,000 concentration.

Experiments 1 and 2 for each day were made as controls. The experiments were arranged in the order of the days on which they were conducted so that the daily controls could be checked against the day's experiments. For each of five groups a new animal was killed, and the experiments and the controls were run simultaneously.

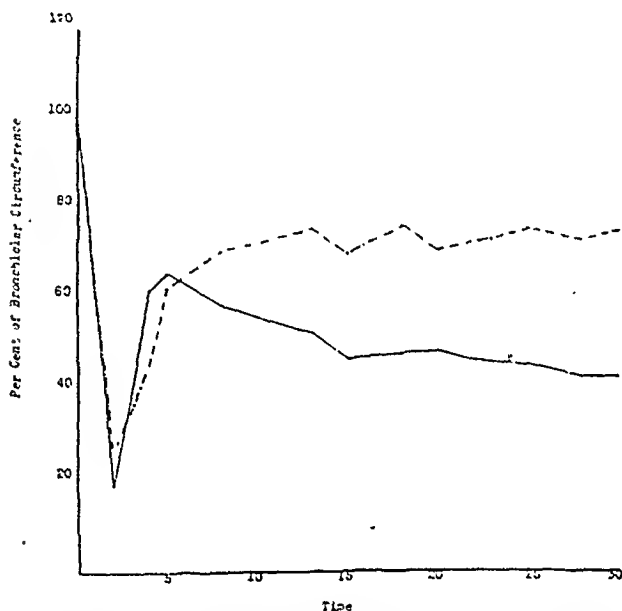


Chart 5 (group 2).—Histamine-antagonistic action of ephedrine ascorbate. Experiment 5: Histamine hydrochloride, one minute; ephedrine ascorbate, three minutes (solid line). Experiment 6: Histamine hydrochloride, one minute; ephedrine ascorbate, three minutes; histamine hydrochloride, fourteen minutes (line of dots and dashes).

The purpose of the experiment was to produce contraction of the bronchiole by adding histamine hydrochloride to the Ringer-Locke-dextrose solution to obtain a 1 : 50,000 concentration. After the contraction due to the histamine was established, and at a fixed interval, the substance to be tested for histamine antagonism was added. Those substances which antagonize histamine allowed the bronchiole to relax and in some instances continued the dilatation above normal. The control tests also showed that there was a spontaneous tendency for the histamine effect to diminish, with a secondary histamine contraction after about fifteen minutes. As a countercheck for histamine antagonism, therefore, two sets of tests were run. In one series, the substance to be tested was added after the histamine contraction had occurred, and the effect was noted. In the other, histamine contraction was produced, the substance added and the histamine antagonism noted; then histamine was again added to see whether the histamine antagonism of the substance would prevent further histamine effect. With substances having histamine-antagonistic properties, then, there would be no or little contraction of the bron-

chiole on the secondary addition of histamine. The controls uniformly showed a secondary contraction

TABLE 6. *Antihistaminic Effect of Ephedrine Hydrochloride*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 7</i>					
Group 2					
Histamine hydrochloride	1:50,000	1	2	5.13	100.0
Ephedrine hydrochloride	1:10,000	3	4	2.30	44.8
			5	2.20	42.8
			8	2.18	42.4
			10	3.01	58.6
			13	3.09	60.2
			15	3.25	63.3
			18	3.87	75.4
			20	3.85	75.0
			23	4.04	78.7
			25	4.08	79.5
			28	4.32	81.2
			30	4.27	83.2
				4.60	89.6
<i>Experiment 8</i>					
Histamine hydrochloride	1:50,000	1	2	5.36	100.0
Ephedrine hydrochloride	1:10,000	3	4	2.48	46.2
			7	2.58	48.1
			10	2.56	47.7
			12	2.35	43.8
				2.62	48.8
Histamine hydrochloride	1:50,000	14	15	2.62	48.8
			17	2.72	50.7
			20	2.85	53.1
			23	2.54	47.3
			25	2.93	54.6
			28	2.15	40.1
			30	2.01	37.5

when the histamine was added for the second time. This double checking system thus provided useful information.

RESULTS OF INVESTIGATION

GROUP 1.—Experiments 1 and 2: These tests were conducted to establish normal as well as his-

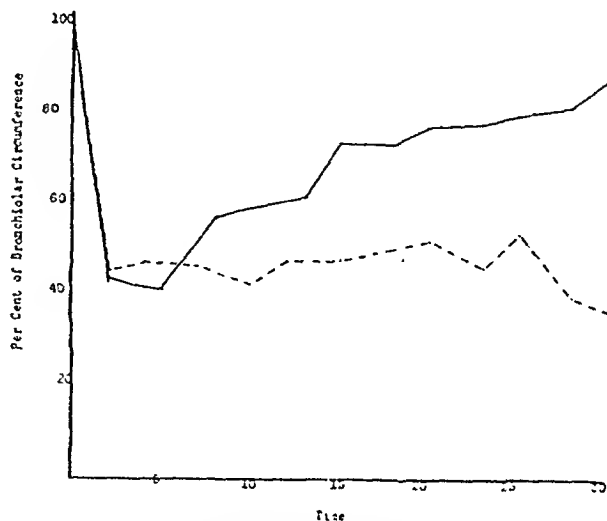


Chart 6 (group 2).—Histamine-antagonistic action of ephedrine hydrochloride. [Experiment 7: Histamine hydrochloride, one minute; ephedrine hydrochloride, three minutes (solid line). Experiment 8: Histamine hydrochloride, one minute ephedrine hydrochloride, three minutes; histamine hydrochloride, fourteen minutes (line of dots and dashes).

mine controls and a subsequent histamine control after twenty-four minutes. Results for 6 normal and 6 his-

tamine controls were plotted and normal and histamine curves established.

On the day of these experiments the normal control maintained a fairly steady bronchiolar lumen, with only gradual contraction. The histamine control showed

TABLE 7. *Antihistamine Effect of Calcium Ascorbate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 3</i>					
Group 3			0	5.50	100.0
Histamine					
hydrochloride	1:50,000	1	3	1.91	34.7
Calcium ascorbate	1:750	4	5	3.91	71.0
			6	4.07	74.0
			8	3.85	70.0
			10	3.44	62.5
			12	3.36	61.0
			15	3.48	63.2
			17	3.49	63.4
			20	3.64	66.1
			23	3.88	70.5
			25	3.92	71.2
			28	3.95	71.8
			30	4.01	72.9
<i>Experiment 4</i>					
Histamine			0	5.56	100.0
hydrochloride	1:50,000	1	3	2.91	52.3
Calcium ascorbate	1:750	4	6	4.92	88.4
			8	4.74	85.2
			10	4.47	80.3
Histamine					
hydrochloride	1:50,000	11	12	3.82	68.7
			15	3.73	67.0
			20	4.38	78.7
			23	4.29	77.1
			25	4.06	73.0
			28	4.14	74.4
			30	4.17	75.0

rapid contraction of the bronchiole with recovery and a second contraction under the continued action of the histamine, thus causing a secondary drop after seventeen minutes.

Experiments 3 and 4: These tests were conducted with the same tissues as those used in experiments 1 and 2. When sodium ascorbate was added after the histamine recovery was slower than in the control, but the histamine antagonism was evident on the addition of the second dose of histamine hydrochloride after fourteen minutes. There was no secondary histamine contraction.

Experiments 5 and 6: The histamine antagonism of vitamin C alone was evident. Here, again, there was a somewhat slower recovery of the bronchiolar lumen, and recovery was maintained, even after a second dose of histamine, although there was a slight contraction for two minutes.

SUMMARY.—The sodium ascorbate and vitamin C did not influence the speed of recovery from histamine contraction but did produce antagonism to the second dose of histamine hydrochloride.

GROUP 2.—On this day controls showed that the bronchiolar lumen maintained its normal size for the whole thirty minutes. The histamine response was strongly active after thirty minutes, indicating that a secondary histamine contraction was obtainable after exposure for this period.

Experiments 3 and 4: Normal recovery from the effect of histamine hydrochloride was slightly inhibited by ephedrine sulfate, indicating that the drug had a slight constricting action on the bronchiole, with little or no antagonism to the second dose of histamine.

Experiments 5 and 6: Ephedrine ascorbate produced prompt recovery from a sharper histamine contraction than that showed in the control, with maintenance of a good level of histamine antagonism after the second dose.

Experiments 7 and 8: With ephedrine hydrochloride there was a decidedly increased histamine contraction as compared with the response with either ephedrine ascorbate or ephedrine sulfate, as well as delayed recovery. Ephedrine hydrochloride is therefore a bronchiole-constricting agent with no histamine antagonism.

SUMMARY.—Ephedrine sulfate caused slight inhibition of recovery from histamine hydrochloride, with little or no antagonism to the second dose of histamine. With ephedrine ascorbate there was quick recovery from histamine and fair antagonism to the second dose of histamine. With ephedrine hydrochloride there was an increase of histamine contraction and no histamine antagonism, rather constriction.

GROUP 3.—Controls for this day showed normal maintenance of the bronchiolar lumen for thirty minutes and an active secondary response to histamine hydrochloride after thirty minutes.

Experiments 3 and 4: Experiments conducted with calcium ascorbate showed a sharp recovery after the

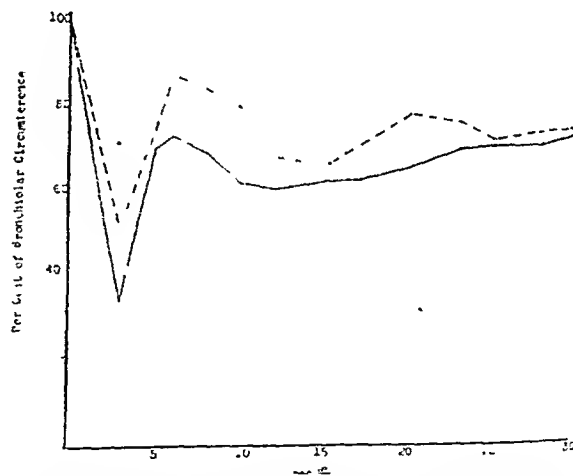


Chart 7 (group 3).—Histamine-antagonistic action of calcium ascorbate. Experiment 3: Histamine hydrochloride, one minute; calcium ascorbate, four minutes (solid line). Experiment 4: Histamine hydrochloride, one minute; calcium ascorbate, four minutes; histamine hydrochloride, eleven minutes.

first histamine contraction, followed by a moderate drop and a moderate rise after the second dose of histamine. This was more rapid than the response with either vitamin C alone or sodium ascorbate.

Experiments 5 and 6: Calcium gluconate showed no histamine antagonism; in fact, it prolonged the action of the drug. The bronchiole did not recover from the histamine contraction for the whole thirty minutes.

SUMMARY.—Calcium gluconate not only did not antagonize histamine hydrochloride, but, in fact, increased contraction of the bronchiole to the drug. Calcium ascorbate, on the other hand, antagonized histamine, and the response was quicker than that to either

TABLE 8. *Antihistamine Effect of Calcium Gluconate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 5</i>					
Group 3			0	6.95	100.0
Histamine hydrochloride	1:50,000	1	3	2.73	39.2
Calcium gluconate	1:1,000	4	6	2.62	37.9
			8	2.79	40.1
			10	2.76	39.7
			13	2.12	30.5
			15	3.54	50.9
			18	3.65	52.5
			20	3.68	52.9
			23	3.63	52.2
			25	3.65	52.5
			28	3.62	52.0
			30	3.63	52.2
<i>Experiment 6</i>					
			0	4.16	100.0
Histamine hydrochloride	1:50,000	1	3	1.79	43.0
Calcium gluconate	1:1,000	4	5	1.91	45.9
			6	1.80	43.2
			10	1.78	42.7
Histamine hydrochloride	1:50,000	11	13	1.65	39.6
			15	1.65	39.6
			18	1.79	43.0
			20	1.81	43.5
			22	1.87	44.9
			25	1.66	49.9
			28	1.83	43.9
			30	1.95	46.8

vitamin C alone or sodium ascorbate. This is significant in view of the conflicting claims made for calcium in the treatment of asthma. It appears from this experiment that the synergistic effect of vitamin C on calcium may be the all-deciding factor in the therapeutic value of calcium in allergy. In fact, calcium gluconate may produce unfavorable results in the treatment of asthma, while calcium ascorbate may be useful.

GROUP 4.—Controls on this day showed fairly normal maintenance of the bronchiolar lumen, as well as a prompt response to a second dose of histamine hydrochloride after twenty-seven minutes.

Experiments 3 and 4: The histamine antagonism of benzedrine ascorbate was followed by active dilatation of the bronchiole. That this dilatation was active was demonstrated by a secondary response to histamine, although the secondary contraction brought the lumen to only a little below normal, and well above the initial histamine contraction.

Experiments 5 and 6: These tests were all the more interesting because benzedrine sulfate gave no such response as did benzedrine ascorbate; in fact, it prolonged histamine contraction and produced virtually no histamine block. Benzedrine sulfate may be considered as bronchiole constricting.

SUMMARY.—In this group of experiments a remarkable difference in pharmacologic action is evident. While benzedrine ascorbate produced a quick recovery from histamine contraction, with strong histamine

block, the benzedrine sulfate showed no histamine antagonism, and in fact prolonged histamine contraction. The implications of this experiment may be important in relation to histamine shock. While benzedrine sulfate can keep a soldier alert, it may predispose him to greater histamine shock, whereas the vitamin C salt may protect against histamine shock.

GROUP 5.—Experiments 1 and 2: The bronchiole used in these controls was sensitive and reacted strongly to histamine, with poor spontaneous recovery; after twenty-one minutes the bronchiole responded with sharp contraction to histamine. The spontaneous recovery from histamine, was only about 44 per cent.

Experiments 3 and 4: Epinephrine ascorbate produced immediate recovery from histamine, with such strong histamine antagonism that the second dose of histamine hydrochloride did not prevent continuation of the bronchiolar dilatation to over twice the normal size.

Experiments 5 and 6: Epinephrine hydrochloride, as was to be expected, produced active recovery from histamine contraction, with moderate dilatation of the bronchiole.

SUMMARY.—One is struck by the remarkable synergistic effect of vitamin C on epinephrine. The epinephrine ascorbate showed about twice the bronchiole-dilating capacity exerted to epinephrine hydrochloride and a much quicker and more active histamine antagonism.

COMMENT

When all five groups of experiments are considered,

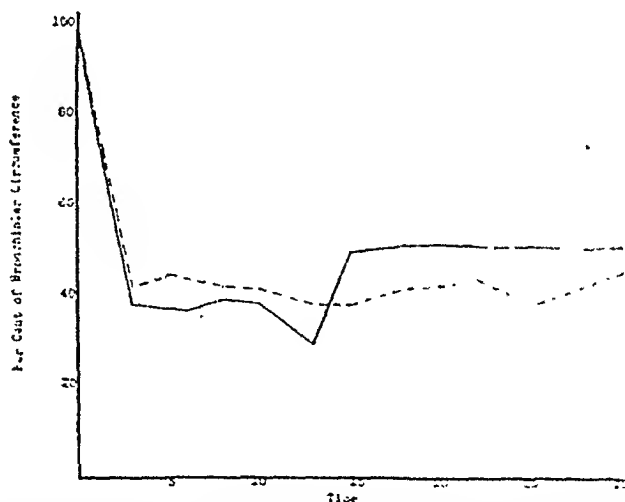


Chart 8 (group 3).—Histamine-antagonistic action of calcium gluconate. Experiment 5: Histamine hydrochloride, one minute; calcium gluconate, four minutes (solid line). Experiment 6: Histamine hydrochloride, one minute; calcium gluconate, four minutes; histamine hydrochloride, eleven minutes (line of dots and dashes).

it may be said that vitamin C (ascorbic acid) has slight histamine antagonism in itself, but when serving as the acid radical for calcium, ephedrine, benzedrine or epinephrine, it enhances their histamine antagonism and bronchiole-dilating capacity. This is essentially important in increasing respiratory ability.

Ephedrine sulfate and ephedrine hydrochloride constrict the bronchioles, while ephedrine ascorbate appears

to have some dilating action. Calcium gluconate exhibits no histamine antagonism; rather, it produces contraction of the bronchiole, while calcium ascorbate shows some anti-histamine action, more than does vitamin C alone or sodium ascorbate. Benzedrine sulfate

TABLE 9. *Antihistaminic Effect of Benzedrine Ascorbate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 3</i>					
Group 4			0	3.36	100.0
Histamine hydrochloride	1:50,000	1	2	0.87	25.8
Benzedrine ascorbate	1:10,000	3	4	1.40	41.6
			2	2.05	61.0
			11	2.97	88.3
			13	3.07	91.3
			14	3.04	90.4
			16	3.10	92.2
			19	3.01	89.5
			21	2.92	86.9
			24	2.96	88.0
			26	3.11	92.5
			29	2.93	87.2
<i>Experiment 4</i>					
Histamine hydrochloride	1:50,000	1	2	0.88	49.7
			3	0.89	50.2
Benzedrine ascorbate	1:10,000	3½	4	0.90	50.8
			5	0.96	54.2
			7	0.88	49.7
			10	1.11	62.7
			12	1.16	65.5
			17	2.42	136.7
Histamine hydrochloride	1:50,000	19	20	2.42	136.7
			22	2.41	136.1
			25	2.37	133.8
			29	1.53	86.4
			32	1.52	85.5

shows no histamine antagonism, but rather prolongation of the histamine effect, whereas benzedrine ascorbate displays pronounced histamine antagonism and bronchiole-dilating properties. Epinephrine hydrochloride shows, of course, strong histamine antagonism, but is only about one-half as active as epinephrine ascorbate, which actually dilated the bronchiole to almost twice that produced by epinephrine hydrochloride.

When approaching such complicated physiological derangements as shock and allergy, one cannot oversimplify the responsible factor by claiming that shock is due to either histamine or adrenalin. The relationship of both histamine and adrenalin to each other constitutes the normal balance and every factor supporting each must be appreciated in order to better understand the restoration of this balance.

The main contribution of this paper is to point out that the amino acids histidine and tyrosin, supplemented by methionine and choline serve as fundamental factors in this balance between histamine and adrenalin. Strangely enough, the amino acid histidine which, when decarboxylated gives histamine, is an antagonist to histamine and can be used clinically to reduce histamine over-action. On the other hand, tyramine, the decarboxylation product of the amino acid tyrosine while the forerunner of epinephrine, also has antagonistic functions to epinephrine. The antagonism between

chemically similar and closely related substances has been strikingly shown by the work of McIlwain. Organisms that require pantothenic acid for growth were inhibited by closely related pantothenic acid analogues. Similar effects occur between paraminobenzoic acid and sulfanilamide and between riboflavin and its analogues.

The value of intravenous or intramuscular amino acid therapy thus becomes readily apparent. The closest study of histidine as well as tyrosine will yield rich results in therapy. The cases here recorded show the clinical use of 4% L(+) Histidine monohydrochloride in treatment of allergy, from asthma and vasomotor rhinitis to migraine. Its use in shock awaits further experimental study.

While histamine received a great deal of attention following its demonstration as the factor in anaphylactic shock and the early work of Dale and Laidlaw, 1910, Kutscher, 1910 and Ackerman, 1910, it was not until 1933 that any therapeutic use for histidine was found. A. G. Weiss and E. Aron described its use in the treatment of gastric ulcer on the theory that a deficiency of the amino acid histidine was concerned in the production and persistence of peptic ulcer. They assumed that they confirmed this on experimental ulcers in dogs.

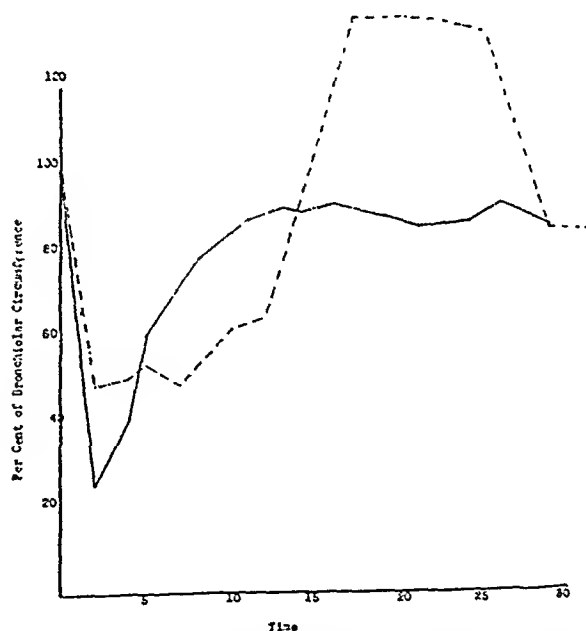


Chart 9 (group 4).—Histamine-antagonistic action of benzedrine ascorbate. Experiment 3: Histamine hydrochloride, one minute; benzedrine ascorbate, three minutes. (solid line). Experiment 4: Histamine hydrochloride, one minute; benzedrine ascorbate, three and a half minutes; histamine hydrochloride, nineteen minutes (line of dots and dashes).

Wide clinical use followed with favorable results reported by D. Smith in 1935 and Eads in the same year.

They described that daily injections of 5 cc. of the 4% solution with the patients on ordinary diet was followed by disappearance of the discomfort, fullness, burning, nausea and vomiting as well as the relief of pain and constipation with return of normal appetite,

increase of weight and striking roentgenologic improvement.

Unfortunately, the explanations for observed clinical reactions are frequently faulty and lead to the discrediting of a procedure that may in itself be useful. Such

TABLE 10. *Antihistamine Effect of Benzedrine Sulfate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 5</i>					
Group 4			0	2.36	100.0
Histamine hydrochloride	1:50,000	1/2	1	1.03	43.6
Benzedrine sulfate	1:10,000	1 1/2	2	1.29	54.6
			4	1.22	51.6
			7	1.23	52.1
			10	1.29	54.6
			12	1.26	53.3
			15	1.26	53.3
			17	1.29	54.6
			20	1.25	52.9
			22	1.22	51.6
			23	1.11	47.0
			25	1.11	47.0
			28	1.01	42.7
<i>Experiment 6</i>					
			0	3.45	100.0
Histamine hydrochloride	1:50,000	1	2	1.07	31.0
Benzedrine sulfate	1:10,000	2 1/2	3	1.62	46.9
			4	2.26	65.5
			7	2.54	73.6
			10	2.86	82.8
			12	2.75	79.7
Histamine hydrochloride	1:50,000	13	14	2.68	77.6
			16	2.19	63.4
			17	2.82	81.7
			22	3.27	94.7
			25	3.27	94.7
			27	3.46	100.2

seems to be the situation with histidine. While K. A. Martin in 1936 and D. J. Sandweiss in the same year, as well as Flood and Mullins showed that results were no better than those obtained with alkali and diet treatment and that there was no constant or marked effect on the acid secretion, nevertheless, the fact that histidine plays an important role in histamine adrenalin balance which is a common denominator in disease escaped attention. The search for a local gastric explanation of histidine effect was necessarily unsuccessful since the histidine therapy attacked the problem at its origin in the sympatho-adrenal mechanism rather than purely locally at the gastric mucosa.

Goodman and Bearg 1938 showed that histidine has no effect whatever on the secretory functions of Pavlov stomach dogs, nor does it alter the tonus or movement of excised intestine, whereas histamine regularly increases gastric secretion and is used as a test for that purpose. This further supports the thesis of this paper that the amino acid histidine does not have the same action as histamine, but rather is antagonistic to its amine, histamine.

In the guinea pig, ten milligrams of histidine produces immediate and complete relaxation of the intestinal contractions provoked by histamine. It also antagonizes the stimulation of excised guinea pig uterus by histamine or pituitrin and generally smooth muscle stimulation by acetylcholine as shown by B. N. Halpern in 1939. One must therefore look to the general anti-

histamine and histamine adrenalin balance effects for the clinical improvement noted from histidine in peptic ulcer by Weiss and Aron as well as Smith and Eads.

How basic the question of histamine adrenalin balance can be is exemplified by the illuminating report of Moon on the vascular and cellular dynamics of shock. "Exactly similar pathologic alterations were seen in the viscera after death from Hg Cl₂ poisoning, eclampsia, intestinal strangulation, acute pancreatitis, burns, and after acute infections of unusual severity. They were also produced experimentally by a wide variety of agents. Our observations indicate that circulatory disturbances of this type may result from various kinds of injury and that in each instance the clinical, physiologic and pathologic features are identical in kind."

"Surgical or traumatic shock presents these same features indicating that capillary atony is a major factor in its development. Other factors also are important; surgical shock represents the summative effects of the disease which necessitated the operation, of psychic and neurogenic factors not yet explained, anaesthesia, hemorrhage, loss of fluid in the region of the operation, and the absorption of products from the damaged tissues."

Moon and his associates began experiments for the dual purpose of testing the effects of absorption from damaged tissues and of studying the morphologic changes seen in viscera after death by shock.

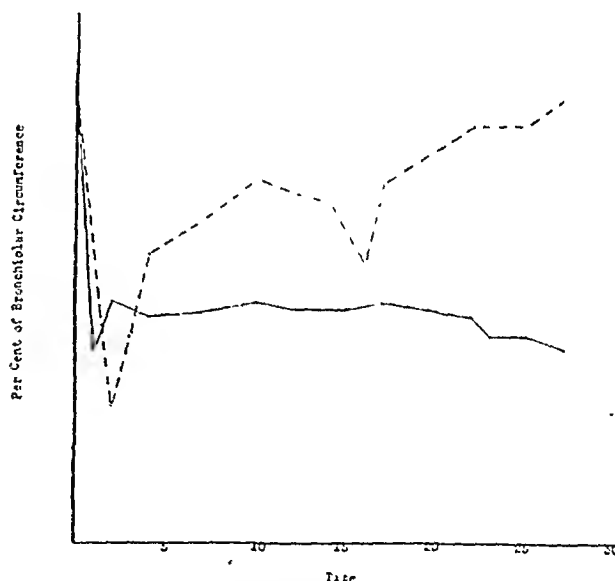


Chart 10 (group 4).—Histamine-antagonistic action of benzedrine sulfate. Experiment 5: Histamine hydrochloride, one-half minute; benzedrine sulfate, one and a half minutes, (solid line). Experiment 6: Histamine hydrochloride, one minute; benzedrine sulfate, two and a half minutes; histamine hydrochloride, thirteen minutes (line of dots and dashes).

The method which they devised to determine whether the absorption of substances from damaged tissues would affect the circulation, was to inject fresh, finely ground, muscle pulp introduced into the peritoneal cavity of normal dogs. This caused progressive circulatory deficiency having all the characteristics of shock. These did not differ in any particular from the effects of extensive burns, histamine, peptone poisoning or ana-

phylaxis. Other tissues as brain, liver or kidney and watery extracts of the tissues mentioned disturbed the circulation in a similar manner.

"By such methods, it was possible to exclude two complicating factors from the conditions of experimentation and evaluate the effects of absorption alone. In each instance shock accompanied by hemoconcentration resulted from the absorption or the injection of the substances mentioned, unaccompanied by the effects of hemorrhage or of anaesthesia."

The visceral appearances after death were indicative of endothelial relaxation in extensive visceral areas. Their first group of experiments gave two significant results. They provided evidence that absorption of products from damaged tissues will produce the complete syndrome of shock independent of hemorrhage and local loss of fluid. They also showed visceral changes,—capillo-venous congestion, stasis, edema, effusions and petechiae, indicating damage to endothelium such as sundry capillary poisons will produce.

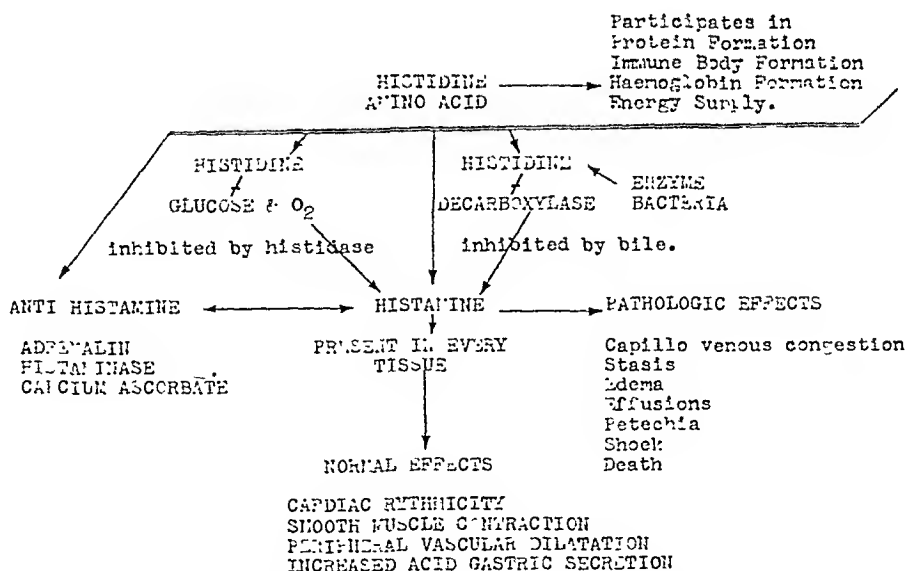
These are fundamentally the train of occurrences in anaphylaxis which is indicative of histamine adrenalin imbalance with predominance of histamine effect. The beneficial effects of intravenous amino acid therapy in the form of protein hydrolysates must be viewed not only from the standpoint of fluid volume and hypo or hyper proteinemia, but also from the angle of histamine adrenalin balance with histamine inhibitions by the histidine in the amino acids administered.

The demonstration that endothelial relaxation was the dominant pathologic occurrence with ensuing capillo venous congestion, stasis, edema and effusion, could also be correlated with calcium and ascorbic acid both factors commonly associated with diffusion of fluids and

intercellular cementum. The fact that calcium ascorbate showed histamine antagonism made them valuable elements in the picture of antihistamine action. Thus histidine combined with calcium ascorbate supplied a mechanism for controlling histamine overaction and stabilizing histamine action. Clinically, the combined use of calcium ascorbate and histidine gave better anti-allergic effect than either alone.

Considering the intimate chemical relationship between histamine and histidine, one might expect that administration of histidine to patients receiving injections of protein antigens might lead to increased histamine output. Yet, in the series of cases here included some which were receiving dust and bacterial vaccine antigens simultaneously with the histidine injections, none showed any sign of increased reactions. Quite the opposite occurred. There were no reactions as the dosages increased and the patients uniformly reported that the first forty-eight to seventy-two hours after the injection they felt particularly well and had a feeling of increased energy and were more at ease. It was usually on the fourth and fifth day that the common feeling of allergic disturbance came more into evidence. This could probably be attributed to the metabolic disappearance of the injected histidine. It was thus possible to demonstrate that histidine could be administered with benefit to allergic patients. This observation opens up the field of usefulness of histidine not only for allergy, but for the whole gamut of pathologic conditions indicating overaction of histamine ranging from shock to intoxications, burns, intestinal strangulation and infections of unusual severity.

A graphic representation of histidine relationship to histamine adrenalin balance may be drawn as follows:



A typical example of normal histamine-adrenalin balance could be described as follows: Impulses, perhaps from the carotid sinus, actuate the sympatho-adrenal system. The discharge of adrenalin stimulates the myocardium, liberates glucose from the liver, increases oxygenation, contracts the peripheral arteries

and mobilizes reserve blood from the spleen and other reservoirs. The increased glucose and oxygen reacts with histidine to form histamine, restores myocardial rhythmicity, dilates the peripheral capillaries, restores gastric secretion and smooth muscle contractility. As long as this interaction occurs, normal balance prevails.

Iwao reports that histamine promotes automaticity in the isolated ox heart, and in strips from the same, and that the histamine content is much greater in the sino atrial node and right atrium than in the non automatic muscle of the left atrium and ventricles. He expresses

TABLE 11. *Antihistamine Effect of Epinephrine Ascorbate*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
<i>Experiment 3</i>					
Group 5			0	3.19	100.0
Histamine hydrochloride	1:50,000	1	2	0.80	25.0
Epinephrine ascorbate	1:1,000	3	4	3.01	94.3
			5	3.45	108.1
			8	4.05	126.9
			10	4.60	144.2
			13	4.78	149.8
			15	5.21	163.3
			18	5.27	165.2
			20	5.41	169.5
			23	5.54	173.6
			25	5.62	176.1
			28	5.18	162.3
			30	5.12	160.5
<i>Experiment 4</i>					
			0	2.27	100.0
Histamine hydrochloride	1:50,000	2	3	0.22	9.6
Epinephrine ascorbate	1:1,000	4	5	1.38	56.3
			6	2.34	103.0
			8	2.05	90.3
			10	2.55	112.3
			13	2.78	122.4
Histamine hydrochloride	1:50,000	14	15	3.13	137.8
			18	3.70	162.9
			20	4.15	182.8
			23	4.13	181.9
			25	5.20	229.0
			27	4.98	219.3
			30	3.30	233.4

the view that the effects of tissue extracts reported by other workers are explicable on their histamine content. The adequate supply of the amino acid histidine is a vital factor on its maintenance. Overaction of histamine is simultaneously inhibited by the amino acid itself. It is interesting to note that Ackerman and Wassmuth found the amino acid arginine a specific antagonist to histamine.

The mechanism of histamine-adrenalin balance can be seen from the experimental work of Went and Martin. After removal of the adrenals when the animals became markedly more sensitive to histamine they also become susceptible to anaphylaxis. The predominant reaction in both brings a fall in arterial blood pressure. Clinically, it was curious to observe that allergic patients generally showed a low blood pressure. After administration of histidine, the patients showed slight to moderate increases in blood pressure, and in one instance where the patient had a hypertension of 160 systolic, after a series of histidine injections, the pressure rose to 200. Those patients who commonly suffered from low blood pressure reported a feeling of increased energy and ability to carry on their work to a greater degree after the administration of histidine.

Aside from the study of histidine in its relation to histamine and its relationship to the sympatho-adrenal mechanics, there are the nutritional and blood forming properties of the amino acid to consider.

Histidine is placed by Eaton and Doty in the list of amino acids which yield extra heat on intravenous administration to the dog. The specific dynamic action (SDA) amounts to about nine calories per gram of extra nitrogen excreted. Histidine is metabolized more rapidly than arginine and has a fifty percent greater calorogenic effect. This aspect of energy metabolism probably explains the clinical experience of increased feeling of energy after the injection parenterally of histidine.

The role of histidine as a glycogen former (in the rat) and its ability to reduce ketonuria was described by Remmert and Butts. Confirming these findings, Featherstone and Berg demonstrated that the deposition of glycogen was at approximately the same rate with L(—) histidine as with equivalent amounts of L(+) glutamic acid. Since histidine is known to be degraded to glutamic acid, the authors suggest that their data admit the possibility that L(+) glutamic acid is formed as an intermediary in the formation of

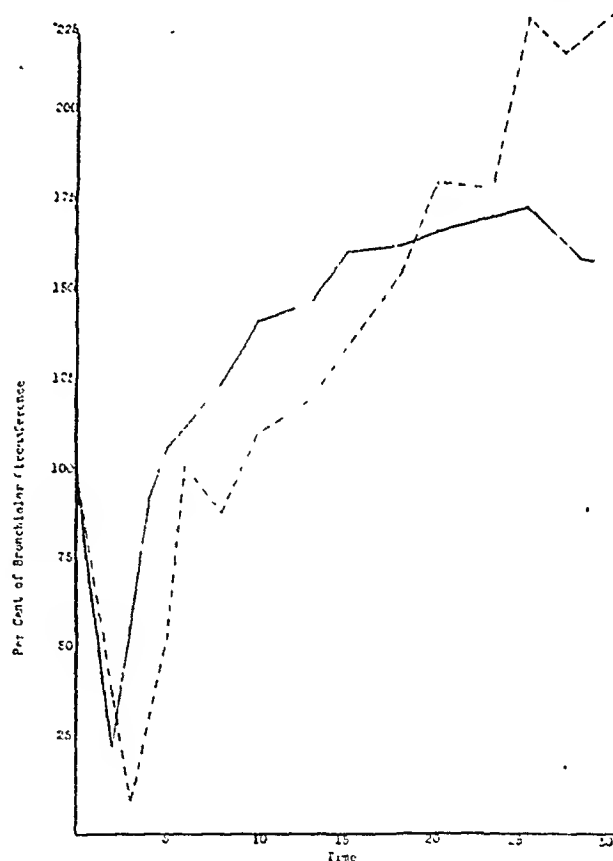


Chart 11 (group 5).—Histamine-antagonistic action of epinephrine ascorbate. Experiment 3: Histamine hydrochloride, one minute; epinephrine ascorbate, three minutes (solid line). Experiment 4: Histamine hydrochloride, two minutes; epinephrine ascorbate, four minutes; histamine hydrochloride, fourteen minutes (line of dots and dashes).

glycogen from histidine. Glycogen formation from L(+) histidine was less than from the L(—) isomer and of doubtful statistical significance.

In pregnancy, the metabolism of histidine appears to play a particular role. According to Weile and Effke-mann, pregnant as compared to non-pregnant women show greatly increased histaminase activity of the blood. It reaches a peak at seven months and then de-

creases. Histidinuria is a characteristic of normal human pregnancy, but is considerably diminished or entirely absent in patients with serious symptoms of preclanptic toxemia. In the latter condition, histamine appears in the urine and is assumed by Kapellar-Adler

TABLE 12. *Antihistamine Effect of Epinephrine Hydrochloride*

Test Substance	Final Concentration of Test Substance	Time of Addition (Min.)	Time of Observation (Min.)	Area Arbitrary Units	Percentage of Original Area
Group 5					
Histamine hydrochloride	1:50,000	1	0	3.47	100.0
Epinephrine hydrochloride	1:1,000	4	2	0.67	19.2
			5	1.26	36.3
			7	1.73	49.8
			10	1.84	53.0
			13	2.38	68.6
			17	3.86	111.2
			20	4.58	132.0
Histamine hydrochloride	1:50,000	14	15	2.25	64.2
			18	2.52	72.6
			20	2.62	75.5
			23	2.82	81.2
			25	3.01	86.4
			28	3.16	91.0
			30	3.21	92.5
			0	4.43	100.0
Histamine hydrochloride	1:50,000	1	3	0.91	26.5
Epinephrine hydrochloride	1:1,000	4	5	2.32	52.5
			7	3.89	87.8
			10	4.19	94.6
			13	4.65	105.6
			15	4.87	109.0
			17	5.05	119.9
			20	5.22	117.8
			23	4.60	103.8
			25	5.11	115.3
			27	4.84	109.2
			30	5.10	115.1

to be a causative factor in the toxemia of pregnancy. Kapellar, Adler and Boxer report that the gonadotropic hormone arrests the histidase activity of the liver, thus apparently affording an explanation for the excretion of histidine by pregnant women. I venture to suggest that the question of dysmenorrhea could be approached for study from this angle since histamine may be a causative factor susceptible to correction by administration of histidine.

Histidine metabolism in pregnancy probably assumes such great importance because of its essential association with blood formation and purine metabolism, both of which play such an important role in connection with nuclei.

We see therefore a wide range of physiologic activity for histidine and a most useful field for therapeutic application which extends from shock and allergy through the range of severe infections to normal metabolism and pregnancy.

The case report here tabulated, gives a rapid view of an already useful clinical application of histidine therapy.

In reviewing this series of cases, a detailed report of the nose and throat findings in each case has been omitted for the sake of brevity. The allergic findings were brought out to show essentially two points; one, that histidine administered along with protein desensitization did not increase sensitivity reactions, but rather diminished them; two, that histidine was valuable as an adjunct.

If the administration of histidine were to lead to an

increase in available histamine, we should get increased reactions. The opposite was found in actual practice. The histidine diminished histamine effect. The second point learned from the case histories is that the parenterally administered effect of histidine is to supply a quickly metabolizable amino acid which led regularly to a feeling of well being and increase in energy. The by effects of relief of constipation and improved gastro intestinal peristalsis was particularly evident in the cases of Meniere Syndrome. The beneficial effects of prostigmin in these cases might well be due to the same type of influence on the gastro intestinal tract.

The mixed protein used for desensitization was a mixed inhalants group and the respiratory vaccine was the Eli Lilly U. B. A. preparation. In each case, the associated nasal sinus condition received the customary routine care. The addition of histidine to the treatment gave a clinical improvement in the patient before the effects of desensitization could be expected to have manifested itself. The histidine was given intramuscularly, at the same time that the protein injections were made. These were given every fifth day, and in some instances, the histidine was given every other day. The effects of the histidine were most marked during the first two days and were less apparent thereafter. After about ten histidine injections, the patients were generally in better frame of mind and reported a feeling of well being that they could recognize as an improvement over previous periods of desensitization.

The histidine therapy is not presented either as a

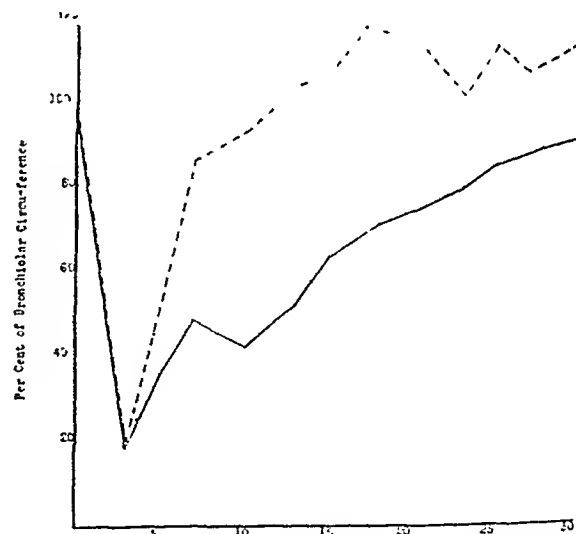


Chart 12 (group 5).—Histamine-antagonistic action of epinephrine hydrochloride. Experiment 3: Histamine hydrochloride, one minute; epinephrine hydrochloride, four minutes; histamine hydrochloride, fourteen minutes (solid line). Experiment 4: Histamine hydrochloride, one minute; epinephrine hydrochloride, four minutes (line of dots and dashes).

substitute for desensitization, or as a cure for allergy, but it does have a distinct role as an adjunct in allergic therapy as in migraine and Meniere Syndrome. Injections of histidine also produce a feeling of well being and energy that should be carefully considered in the care of the post-operative patient and in shock. The injections were given intramuscularly; 5 cc of the 4% solution being employed.

CONCLUSION

1. A role of therapeutic usefulness of the amino acid histidine is indicated in allergic and related conditions.
2. Histidine is antagonistic to histamine and plays an important part in histamine-adrenalin balance in shock.
3. Histidine produces a feeling of well being and

energy that could be useful in the care of post-operative patients and the treatment of shock.

4. Further study of histidine enrichment of parenterally administered protein hydrolysates as blood substitutes is being conducted.

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CASE REPORTS

Name	Sex	Age	Chief Complaint	Allergic to	Treatment	Reaction
1 A.H.	F	25	Persistent sneezing; watery nasal discharge. Hay Fever.	Dust 3+ Feathers 1+ Egg White 1+ Chocolate 2+ Milk 2+	Mixed Protein and respiratory mixture. Histidine.	Sneezing ceased after third injection. Has feeling of well being
2 E.B.	F	38	Chronic Sinusitis Post-nasal drip Asthma	Dust 4+ Milk 4+ Feathers 4+ Chocolate 4+	Mixed Protein and respiratory mixture. Histidine Rt. antrum washed-neg.	Breathing easier. Asthma relieved. More "pep"; post- nasal drip diminished.
3 G.C.	F	35	Post-nasal drip with odor. Headaches; pain in knees and elbows; generally tired. Chronic Asthma.	Sensitive to eggs, feathers (in child- hood). Dust 4+ 4+	Mixed Protein and respiratory mixture. Histidine. Rt. Antotomy.	Headaches ceased. Tired feeling gone. General feeling of well being. Asthma relieved.
				Received desensitiza- tion previously without relief.		
4 J.L.	M	59	Chronic Sinusitis Asthma	Feathers 3+ Dust 2+ Milk 2+	Mixed Protein and respiratory mixture. Histidine. Left an- trum washed three times.	Breathing easier. Feels better than he has in five years.
5 F.C.	F	35	Hay Fever. Sneezing- nasal obstruction. Urticarial attacks.	Generally allergic to foods and inhalants. Had several courses of desensitization at various hands with- out benefit.	Histidine Cal. Cev- itamate.	Feels much better. Nasal membrane less congested; sneezing and coughing greatly diminished.
6 L.B.	M	41	Recurrent colds Nasal obstruction; post-nasal "drip".	Dust 3+ Feathers 2+	Mixed Protein and respiratory mixture. Histidine.	Feeling of well being; post-nasal drip disap- peared; nasal obstruc- tion improved.
7 J.B.	M	51	Sneezing; nasal obstruction; stuffiness in ears; rhinorrhea.	Dust 4+	Dust (conc.) Histidine.	Breathing easier. Feels better than with any other medication he has taken.
8 L.R.	F	41	Severe migraine headaches	Dust 4+ Feathers 4+ Chocolate 4+ Sulfathiazole severe reactions.	Histidine.	Color improved. Headaches not as severe or as often. Longest period of freedom from attacks.
9 R.W.	M	16	Asthma (since early childhood) post-nasal drip	Dust 4+ Feathers 4+ Milk 4+ Chocolate 2+ Egg White 2+	Mixed protein and respiratory mixture. Histidine. Both an- trums washed-4x.	Face cleared. Eczemic patches disappearing. Asthmatic attacks less frequent.
10 J.S.	M		Nasal obstruction	Dust 4+ Feathers 2+ Chocolate 1+ Milk 1+	Mixed protein and respiratory mixture. Histidine.	Feeling of well being. Nasal obstruction relieved.
11 S.R.	M	50	Nasal obstruction; sneezing; watery nasal discharge	Dust 3+ Chocolate 1+	Mixed protein and respiratory mixture. Histidine.	Generally improved.
12 H.H.	M	55	Pain in left arm Pain in right knee Muscle tonus dis- turbance		Ganglion application. Histidine.	Able to move arm much easier. Gener- ally, feeling of well being.
13 P.H.	F	15	Vasomotor Rhinitis since age of five. Severe nasal obstruction.	Dust 4+ Most foods	Mixed protein and respiratory mixture. Histidine.	Breathing easier. Nasal obstruction greatly relieved.

CASE REPORTS—(Continued)

Name	Sex	Age	Chief Complaint	Allergic to	Treatment	Reaction
14 R.R.	F	21	Susceptible to colds; nasal obstruction; rash on hands.	Dust 4+ Furs 2+ Chicken 3+ Cauliflower 3+ Peas 3+ Wh. Potato 3+	Mixed protein and respiratory mixture. Histidine.	Feels better than she has for some time. Rash on hands disap- peared.
15 A.P.	M	25	Nasal obstruction. Rhinorrhea. Hay Fever —9 yrs. Recurrent nasal polypi.	Wheat 1+ Feathers — Dust 4+ Orris Root 2+ Tobacco —	Mixed protein and respiratory mixture. Histidine. Removal of polypi.	General feeling of well being. Dimin- ished rhinorrhea.
16 V.S.	F	42	Nasal obstruction; sneezing; repeated colds.	Feathers 4+ Egg White 2+ Chocolate 2+ Coffee 2+ Dust 4+	Dust (conc.) Respiratory mixture. Histidine.	Sneezing ceased. Feeling well. Nasal obstruction relieved.
17 S.D.	F		Noise and stuffiness in right ear; severe attacks of vertigo and deafness (Merriere Syndrome)	Not allergic	Histidine inflation.	Better reaction than to previous therapy
18 B.T.	F	40	Noise in right ear; severe attacks of vertigo and deafness (required hospitaliza- tion and study) Meniere Syndrome.	Not allergic	Histidine with pros- tigin 1-2000 tubal treatment.	Feeling of well being. Constipation relieved. Normal peristalsis; relief of attacks following therapy.
19 W.K.	M	68	Stiffness of neck Weakness of voice Nasal obstruction	Not allergic	Histidine ganglion treatment	Relief of stiffness. Improvement of aphonia. Feeling of well being.
20 A.R.	F	42	Hay Fever; recurrent colds; nasal obstruc- tion; tiredness.	Ragweed 4+	Histidine. Cal. Cevitamate. Nasal treat.	Relief of nasal ob- struction and feeling of energy recovery.
21 J.R.	M		Severe itching of ear and rectum. Eczema of auditory canals.	Dust 4+ Feathers 3+ Chocolate 3+	Mixed protein and respiratory mixture. Histidine.	Itching lessened. Blood pressure rose from 160/110 to 200/140. Therapy stopped.
22 T.P.	F	41	Sneezing; nasal obstruction; post nasal "drip".	Dust 4+ Milk 4+ Egg White 4+	Mixed protein and respiratory mixture. Histidine.	Sneezing diminished. Nasal obstruction has disappeared. Feels well and better than customarily.
23 C.B.	F	38	Has had during last 7 mos. recurrence of herpes of upper lip and nostril with severe vasomotor imbalance with flushing and spotting of skin.	Reacts strongly to all protein tests.	Histidine.	Has had years of previous treatments of wide variety with strong reactions. Had best effects from Histidine.
24 I.B.	F	45	Headaches; generalized tired feeling; periodic nasal obstruction.	Not allergic	Histidine. Nasal treatment.	Attack of diarrhea and kidney stone colic. Therapy discontinued.
25 R.B.	F	35	Pain in right max- illary region. Eczema of external auditory canals.		Histidine. Rt. antrum washed.	Relief of maxillary pain and improve- ment of eczema.
26 J.H.	M	39	Rt. migraine headache, 8-10 years. Nasal obstruction.	— —	Ganglion block, Histidine. Rt. antrum wash- negative.	Marked relief of migraine attacks. Has had only few mild attacks since treat- ment

The Role of the Fat Soluble Vitamins A and D in Nutrition*

The Requirements of Vitamin A

By

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THE REQUIREMENTS OF VITAMIN A
THERE IS some difference of opinion as to the minimum requirements of vitamin A necessary for the human organism. Using the amount of vitamin A necessary to prevent hemeralopia in the adult, Booher (*Booher, L. E. Vitamin A Requirements and Practical Recommendations for Vitamin A Intake, J.A.M.A. 110:1920, 1938*) found that in the adult twenty to thirty International Units per kilo were essential. Thus for an adult weighing seventy kilos (150 lbs.) the minimal requirements per day would be between 1,400 to 2,000 units. For the growing child demanding additional vitamin A to cover the requirements of growth Booher suggested 6,000 to 8,000 units per day and 5,000 units per day for the pregnant or nursing woman. Jeghers (*Jeghers, H. The Degree and Prevalence of Vitamin A Deficiency in Adults with a Note on Its Experimental Production in Human Beings, J.A.M.A. 109:756, Sept. 4, 1937*) on the basis of his experimental work with medical students stated that a larger amount of vitamin A, namely 4,000 units per day, was the essential minimum. He furthermore recommended that the minimum quantity, as a factor of safety be 6,000 units per day. The larger amount obviously gives increased assurance that the requirements of health will be met, and is particularly preferable since there is no evidence of any toxic effects from the larger dosage.

The Technical Commission for the Study of Nutrition of the Health Organization of the League of Nations has recommended 2,000 to 4,000 units a day for an adult and an amount equalling 6,000 to 8,000 units a day for growing children between the ages of two and fourteen years. This amount of vitamin A may be best obtained from milk, eggs, butter, green leafy vegetables as well as a liberal supply from fish liver oils. The amount of vitamin A recommended for pregnant and nursing mothers is a minimum of 5,000 International Units a day, also to be obtained from the foods mentioned as well as supplementary amounts from the addition of fish liver oil to the daily diet.

The National Research Council (Recommended Dietary and Allowances, page 3, May, 1941; Committee on Foods and Nutrition) published the following table of Daily Requirements of Vitamin A:

MAN (70 Kg.)	5,000 Int. Units
WOMAN (56 Kg.)	5,000
Pregnancy, latter half	6,000
Lactation	8,000
CHILDREN	
Under 1 year†	1,500

1-3 years‡	2,000
4-6 years . . .	2,500
7-9 years . . .	3,500
10-12 years . . .	4,500
GIRLS	
13-15 years	5,000
16-20 years	5,000
BOYS	
13-15 years	5,000
16-20 years . . .	6,000

Liberal amounts of vitamin A should also be supplied to the infant particularly if artificially fed or prematurely born, one of the reasons being that the liver of the newborn contains only minimal amounts of stored vitamin A.

The significance of ample vitamin A intake well above the minimal requirements for the promotion of superior physical development is summarized by Sherman as follows:

"The evidence now at hand in the case of vitamin A, indicates that those dietaries giving the best results are those whose vitamin A values are several fold higher than the intakes which would just cover the readily demonstrable actual need. To obtain the fullest measure of benefit, in the experiments of Mellanby and Green, requires four times the intake of vitamin A value which sufficed to support normal growth and every appearance of normal health. In Batchelder's investigation of the influence of the different levels of vitamin A feeding upon the nutritive welfare of experimental animals throughout their lives and into the second generation, it appeared that the best all round results were obtained only when the vitamin A value of the food was four times as high as was demonstrably necessary to support normal growth and all the visible indications of good health."

The importance of a rich store of vitamin A for survival was shown by Sherman and Cammack (*Sherman, H. C. and Cammack, M. L. A Quantitative Study of the Storage of Vitamin A, J. Biol. Chem. 68 69-74 1926*) on the basis of the following experimental observations. If rats of the same age were maintained on diets containing different levels of vitamin A, those animals survived the longest after the withdrawal of vitamin A whose previous diet had contained the larger amount of the vitamin, although the relationship did not exhibit an accurate arithmetical proportion. The important fact is that increased amounts of vitamin A

* Requirement may be less if provided as Vitamin A, greater if provided chiefly as the provitamin carotene.

† Needs of Infants increase from month to month. The amounts given are for approximately 6-8 months.

‡ Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

* Continued from June issue
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in the diet, do encourage the laying up of a more ample reservoir of this food factor, which may be drawn upon in times of increased need or deficient intake.

An indication of the desirability of ample administration of vitamin A in the newborn is indicated by the fact that the reserves of the vitamin during this period are quite low (Dann, W. J. *Transmission of Vitamin A from Parents to Young in Mammals: Effect of the Liver Reserves of the Mother on the Transmission of Vitamin A to the Foetal and the Suckling Rat*, *Biochem. J.* 28:2141, 1934). Dann showed that there was some relationship between the amount of vitamin A in young rats at the end of the suckling period and the vitamin A reserve of the mother.

There is no evidence at the present time that large amounts of vitamin A well in excess of the accepted requirements are capable of producing any harm.

The value of rich sources of vitamin A as supplements to our usual diet, is shown by the following facts. Left to their ordinary choice, families spending the same amount of money for food, may show a great difference in the amount of vitamin A in the foods purchased, being four to five times as great with some families as with others (Gillett, L. H. and Rice, P. B. *Influence of Education on the Food Habits of Some New York Families*, N. Y. Assoc. for Improving the Condition of the Poor, 1931). Thus some diets were found to contain 18,000 units of vitamin A. These diets were about twenty-two times as rich in vitamin A as other diets which contained only 800 units.

As a result of the education of families in the importance of various foods in the diet, there was an increase of 21 percent in vitamin A content over those diets among people who had not received the benefit of such instruction. The increased amount of vitamin A in the diet bore no definite relationship to the money spent on food, some of the less costly diets in individuals who chose wisely containing more vitamin A than in the case of many other diets which cost considerably more but in which the choice of foods was less intelligently planned.

There are other reasons which indicate the value of supplementary additions of vitamin A above and beyond that important for minimal health standards. First, is the factor of safety, since excess vitamin A stored primarily in the liver, helps to tide over an individual when there may be actual depletion in the ingestion of available sources of this vitamin. This may conceivably occur during periods of illness associated particularly with anorexia and vomiting and disturbances of absorption from the alimentary tract, as in some intestinal disorders. Hyperactivity of the intestinal tract, as occurs in various diarrhoeal states may also lead to deficient absorption and utilization of vitamin A. A reserve source built up through previous liberal intake of vitamin A may under such circumstances stand in good stead, and carry the individual through this critical period.

Secondly, even in the absence of such unpredictable vicissitudes which may make demands on vitamin A stored during normal health, an excessive amount of vitamin A intake, may be valuable in maintaining a

superior state of nutrition. Batchelder (*Batchelder, E. L. Nutritional Significance of Vitamin A Throughout the Life Cycle*, *Am. J. Physiol.* 109:430-435, 1934) on the basis of animal experimentation, showed that not only the animals themselves but their offspring, were benefited nutritionally when the vitamin A intake was increased to four times that required for minimum standards of physical adequacy. In her experiments on rats she noted that with each decrease in the amount of vitamin A, there was a definite decrease in survival, with slower growth and less weight at all ages. In addition there was a definite decrease in the duration of reproductive life.

The treatment of vitamin A deficiency depends on a diet containing sufficient amounts of vitamin A, to which may be advantageously added fish liver oils and particularly, halibut liver oil commercially prepared concentrates. In this manner very large quantities of vitamin A may be administered in very small bulk and in a readily absorbable form. In the presence of definite vitamin A deficiency, the importance of giving large amounts of the vitamin in single doses has been recognized clinically. Thus in Fisher's case (*Fisher, O. E. Severe Night Blindness Due to Vitamin A Deficiency*, *Brit. M. J.* 2:944, 1938) of night blindness in a young boy, a definite clinical response was obtained one hour after the administration of a single dose of 36,000 International Units of vitamin A. This comparatively large amount of vitamin A was administered in four capsules of halibut liver oil. Following this the treatment was then continued with the administration of four capsules of halibut liver oil, three times a day with still further improvement of his visual acuity in a darkened room. His skin which was originally very dry with numerous black keratinous plugs which blocked the sweat glands, showed great improvement. It became smooth and moist and most of the horny plugs disappeared. He also gained eight pounds in weight.

The prompt effect of large doses of vitamin A in the cure of night blindness is also shown in the report of Vaillant and Gillis (*Vaillant, C. and Gillis, L. Night Blindness Treated with Vitamin A*, *Lancet*, 236:149, 1939). The daily administration of 10,000 International Units of vitamin A caused improvement of almost total night blindness in a girl in two weeks.

The disappearance of skin lesions due to vitamin A deficiency by the administration of large amounts of vitamin A is less prompt than is the curative effect in night blindness.

The role of vitamin A in hyperthyroidism is of considerable interest. There is experimental evidence which suggests that the amount of vitamin in the blood is markedly reduced in the presence of exophthalmic goiter (Wendt, H. *Ueber Veränderungen im Karotin-Vitamin-A-Haushalt beim Myxödem und bei Kretins*, *Munch. Med. Wchnschr.* 82:1679, 1935). In the treatment of this disorder Wendt therefore administered as much as 50,000 to 80,000 units of vitamin A three times a day.

An important reason for increasing the amount of vitamin A above the normal requirement in the case of pulmonary tuberculosis is shown by the work of Breese,

Watkins and McCoord, (*Breese, B. B., Jr., Watkins, E. and McCoord, A. B. The Absorption of Vitamin A in Tuberculosis. J.A.M.A. 119:3-4, May 2, 1942*). They found in a group of twenty-nine patients suffering from severe degrees of pulmonary tuberculosis with associated intestinal symptoms, that the absorption of vitamin A was poorer than in a group of normal individuals. The more serious the intestinal symptoms, the more marked was the inability to absorb vitamin A.

In the diet of the individual suffering from pulmonary tuberculosis there is thus a good experimental basis for increasing the vitamin A content of the diet. In the presence of associated intestinal symptoms the vitamin A in the diet should be even more liberal in amount.

While deficiency of vitamin A may well be a factor in making the individual a prey to infectious disease, the proof is not clear that the administration of large doses of vitamin A during the course of an infection has any definite effect on the disease in the absence of such primary deficiency. The important fact is that every effort should be made to assure the individual an ample supply of vitamin A, in order to avoid a deficiency state which may secondarily increase the susceptibility of the individual to respiratory and other infections.

Although the importance of vitamin A in nutrition is of course unquestioned, tremendous increase in the amount, doses in excess of 100,000 units a day have produced pathological changes in the 50 gm. rat for a period of one hundred days unless the animal died earlier. (*Vedder, E. B. and Rosenberg, J. Concerning Toxicity of Vitamin A. J. Nutrition. 16:57, 1938*). Since the average vitamin A requirement of the adult is about 5,000 International Units per day, the danger of hypervitaminosis can be ignored.

Regarding the importance of generous amounts of vitamin A, Booher (*Booher, Lela, E. The Vitamins: Vitamin A Requirements and Practical Recommendations for Vitamin A Intake, Pg. 112 and 114, 1939. A.M.A.*) has written as follows:

"It is quite generally conceded that the most careful control of experimental laboratory animals has not been rewarded by uniformity of response to graded intakes of vitamin A. This being the case with so well standardized an animal as the rat has now come to be, one may logically expect even greater physiologic variation in the vitamin A requirements of human beings. The only practical solution to the problem is to allow a generous margin of safety over any estimate based on studies of human subjects necessarily limited in number. . . .

"It must be concluded that our knowledge of the factors which affect the utilization of the vitamin A activity of foods and of the physiologic conditions which may alter these is for the present very limited. Since it is customary to evaluate the vitamin A content of diets on the basis of biologic assay values as determined with laboratory animals (rats) and without regard to the particular vitamin A or carotene sources, the practical solution lies in providing for liberal amounts of vitamin A in the human diet. . . .

"Experimentation with animals has shown quite conclusively that liberal allowances of vitamin A over and above the daily requirement which will support normal dark adaptation, an average growth rate and an outward thrifty physical condition, are essential for maintaining bodily reserves of vitamin A and for the successful bearing and rearing of young. Experiments with animals have shown that a liberal intake of vitamin A is also conducive to longevity and to prolonging the prime of life. . . ."

Vitamin A is therefore of crucial importance in nutrition. Natural vitamin A is more readily absorbed than its precursors, the carotenes. The fish liver oils are an excellent and dependable source of the natural vitamin A. The amount of vitamin A obtainable from such sources as green and yellow vegetables, milk, eggs and butter is considerably less than that in fish liver oil. Reinforcement of these sources by fish liver oil of standardized potency may therefore at times be extremely useful. Halibut liver oil is the richest available source of vitamin A.

An ample supply of vitamin A is essential for optimal growth, and for the prevention of epithelial metaplasia, which among other alterations of structure, may cause pathological changes interfering with nature's defense against infection. Vitamin A is important in the maintenance of visual integrity and the prevention of the earliest and most subtle evidence of hemeralopia, as well as the more serious complications of xerophthalmia with ultimate blindness. It plays a major role in assuring normal reproductive function.

Larger amounts of vitamin A may be essential in disorders associated with disturbed intestinal absorption, in some infectious processes, in the presence of liver pathology and perhaps in thyroid disease with a low plasma concentration of vitamin A. When frank disorders of a vitamin A deficiency state exist, as exemplified by the changes described in the text large doses of vitamin A are indicated well beyond those essential for the maintenance of normal health.

(To Be Continued in August Issue)

A New Test For Gastric Function*

By

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THE exploration of gastric function is of undeniable importance for a well established gastroenterologic diagnosis. There is no right to exact from the test for gastric function the surety or efficiency we are not in condition to expect from any other method of diagnosis, including those of technical order. On the other hand, among the innumerable functional tests, let them be hepatic, pancreatic, renal etc., there does not exist any other that can be compared with the gastric test in its importance.

Lately, the histamine test has permitted a better study of the hydrochloric acid and peptic secretion, improving the analysis of the gastric juice. Nevertheless, its use has been restricted through fear of general reactions and because at other times it has to be given parenterally. In this respect, we have practiced for some time past in the National Dispensary for diseases of the digestive apparatus "Priscol," an imidazoline compound, something similar chemically and physiologically to histamine and which could constitute an excellent stimulant for gastric secretion, and efficiently replace histamine, without its disturbances but including its advantages. On the other hand, its oral application is practicable.

METHOD AND TECHNIQUE

We carried out a double study on the action of this new imidazoline compound, one local and one general or parenteral, using in all cases elemental proofs such as Erhmann's food test (96.155 cc. alcohol and 275 cc. of distilled water) and hydrochloride histamine in doses of 1 milligram. We selected patients with apparently healthy stomachs and others with already established lesions. In all of them we carried out four kinds of exams in different periods of time, in some cases taking advantage of analysis that had been practiced before our experience. The first examination or test, is by the use of a simple sound while fasting and a fractional analysis without any kind of stimulant or food. The second exam is by using Erhmann's food test. The third exam is by using 1% or 2% solution of Priscol if applied orally, or in an amp. of 1 cc. of Priscol solution containing 10 mg. of the substance in the case of investigating the parenteral action.

The technique which we practice in extracting the gastric juice and in administering the preparation which we have studied is the following: slow and smooth introduction of a simple sound, or better still

the gastroduodenal sound, or our modification of the triple sound salivogastroduodenal). Having placed the sound, the gastric juice is extracted with a 20 cc. syringe or in the case of working with the double or triple sound by the use of an aspirator. Having extracted the first sample of the secretion while fasting, a 1% or 2% solution of imidazoline to 50 or 100 cc. is poured through the sound; or in the case of studying the parenteral action an amp. of 10 mg. of Priscol in 1 cc. solution is injected subcutaneously or intramuscularly. In the case of using the local application, it is convenient when placing the substance to aspirate several times with the object of properly mixing the stimulant solution with the gastric juice. From the moment the solution is introduced through the sound or the substance is injected, we extract samples every half-hour up to two hours. In each sample the quantity, colour, aspect, mucus, blood and bile is studied (when using the simple sound) free and total combined acidity, and lastly a microscopic analysis is carried out. Through want of space we have only transcribed part of the cases studied and we have considered only quantity and free and total acidity.

LOCAL APPLICATION ACTION

Basing comparison on the cases already studied, and carrying out a comparative analysis on the action of the imidazoline solution with respect to Erhmann's food test or hydrochloric histamine test by parenteral use, we have come to the following conclusions:—1) Introducing through the sound 50 to 100 cc. of a 1% or 2% Priscol solution in a volume of 300 cc. of distilled water, this exercises a remarkable action on the hydrochloric and pepsic secretion of the stomach. 2) No general or local kind of reactions have been noticed. 3) Comparing the Priscol oral test with Erhmann's alcoholic food or with caffeine solution, we find that it is superior particularly in respect to acid values. 4) The gastric secretion obtained by Priscol presents a limpid or translucent colorless aspect, containing mucus abundantly. 5) The highest acid values were those obtained in about 120 minutes. 6) With respect to the histamine test by parenteral use, the diagram in general showed a decline and the highest acid values appeared more tardily. (x)

PARENTERAL ACTION

The parenteral use of Priscol as compared with the histamine showed an action resembling the histamine, (see table on next page.) Both the quantity of the secretion as well as the acid values, free and total acidity, were in general similar, in some cases in which histamine produced a greater free acidity as well as a major secretion and in other cases quite to the contrary,

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From: National Dispensary for Diseases of the Digestive Tract.

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x See also: J. Nasio. *Prensa Med. Arg.* 1943-30.

the Priscool produced an acidity and secretional quantity far superior to that obtained with histamine. It is important to note that the maximum of the acidity level has been obtained within a time period similar to that of histamine, that is between 60 and 90 minutes. Among the studied cases recorded were found free acid values that oscillated between 0 to 115 cc. n/10 NaOH,

2-Bencil 4-5 imidazoline or Priscool Test by Parenteral Use

No.	Diagnostic	Characters	Time in minutes				
			0	30	60	90	120
1	Dyspepsia	Quantity	5	12	5	12	5
		Free acidity	16	19	8	19	16
		Total acidity	20	28	12	28	20
2	Duodenal ulcer	Quantity	15	20	15	20	15
		Free acidity	38	80	105	80	65
		Total acidity	51	100	125	105	82
3	Ulcerous syndrome	Quantity	20	10	25	10	17
		Free acidity	0	65	10	105	115
		Total acidity	20	110	51	135	118
4	Gastritis	Quantity	7	3	3	7	7
		Free acidity	0	0	0	0	0
		Total acidity	9	8	6	12	14
5	Duodenitis	Quantity	45	30	15	20	25
		Free acidity	89	65	91	54	0
		Total acidity	120	90	120	66	26
6	Hypochylia	Quantity	10	15	20	10	10
		Free acidity	0	0	0	15	10
		Total acidity	21	28	22	30	22
7	Duodenal ulcer	Quantity	20	8	10	10	5
		Free acidity	0	0	26	70	46
		Total acidity	10	20	36	101	70
8	Gastric allergy	Quantity	8	10	11	13	8
		Free acidity	0	0	10	30	19
		Total acidity	5	20	20	44	29
9	Duodenal ulcer	Quantity	11	30	35	8	12
		Free acidity	0	0	0	0	26
		Total acidity	10	12	13	7	33
10	Colitis, hyper-aesthetic syndrome	Quantity	20	25	25	15	15
		Free acidity	60	0	55	40	30
		Total acidity	82	30	70	61	60
11	Abdominal ptosis	Quantity	10	10	5	7	14
		Free acidity	0	0	0	0	0
		Total acidity	15	20	10	15	9
12	Cholecystitis	Quantity	25	10	20	20	25
		Free acidity	0	0	43	20	20
		Total acidity	16	22	60	60	36
13	Colitis	Quantity	13	15	7	11	14
		Free acidity	0	0	0	0	0
		Total acidity	5	5	11	14	14
14	Ulcerous syndrome	Quantity	20	20	5	12	10
		Free acidity	85	40	30	75	56
		Total acidity	113	52	42	85	81
15	Periduodenitis	Quantity	9	10	8	6	5
		Free acidity	0	0	4	18	19
		Total acidity	7	5	12	26	24
16	Colitis	Quantity	10	15	30	15	20
		Free acidity	0	0	15	47	34
		Total acidity	14	12	36	67	48
17	Duodenal ulcer	Quantity	20	15	18	15	15
		Free acidity	0	0	0	0	0
		Total acidity	13	10	7	11	10
18	Ulcer of the small curvature	Quantity	40	7	6	5	10
		Free acidity	21	19	8	9	8
		Total acidity	33	11	5	2	6
19	Lumbago	Quantity	8	9	14	10	7
		Free acidity	0	14	42	19	17
		Total acidity	8	19	45	25	23
20	Duodenal ulcer	Quantity	11	20	25	22	20
		Free acidity	15	28	45	32	30
		Total acidity	21	37	54	40	32
21	Paralysis of the right steno pseudo mastoidens	Quantity	6	6	7	10	10
		Free acidity	0	0	22	35	38
		Total acidity	12	13	34	60	68
22	Cholecystitis and Gastric atrophy	Quantity	9	10	12	11	10
		Free acidity	0	0	5	6	3
		Total acidity	6	7	12	12	10
23	Megacolon	Quantity	15	10	14	15	10
		Free acidity	10	18	25	24	22
		Total acidity	19	26	33	30	29
24	Duodenal ulcer	Quantity	10	12	10	14	10
		Free acidity	0	0	0	20	0
		Total acidity	18	20	12	35	10
25	Colitis, irritable colon	Quantity	16	6	17	10	10
		Free acidity	0	10	22	35	38
		Total acidity	12	13	34	60	60
26	Ulcer of the juxta-cardiac region	Quantity	15	10	18	15	10
		Free acidity	15	23	34	30	28
		Total acidity	35	38	40	37	35
27	Gastritis	Quantity	10	15	25	10	10
		Free acidity	0	0	0	15	10
		Total acidity	21	28	22	30	22
28	Gastric ulcer	Quantity	20	25	19	15	10
		Free acidity	15	30	48	35	28
		Total acidity	27	43	56	49	39
29	In observation	Quantity	18	20	25	10	14
		Free acidity	10	18	32	38	25
		Total acidity	19	25	43	50	43

the values of 30 to 60 being more frequent. It is a detail of much interest that in several cases of "so-called"—anaecidity histamine resistant—we obtained with Priscool, free hydrochloric acid. The diagram results on gastric acid obtained with Priscool solution either orally or by parenteral use are in part similar to those of Adams (1) or Stalder (2).

CONCLUSIONS

1) The hydrochloric solution of 1% or 2% 2-Bencil 4-5 imidazoline (Priscool) in a volume of 300 cc. of distilled water given through the sound or the same preparation given in an amp. of 10 mg. is capable of producing diagrammed gastric secretion of such value that the practice constitutes an excellent method for the test on gastric functioning.

2) The gastric secretion obtained by local application (sounding) is far superior in quantity and quality to that obtained by Erhuann's food test or by caffeine but inferior to what is obtained by histamine in injections.

3) The highest acid values obtained with the oral test are those obtained in between 90 and 120 minutes, while with histamine they appeared between 30 to 90 minutes.

4) By injecting 10 mg. of Priscool the parenteral way, a secretion is obtained which is very superior in quantity and quality to the alcoholic food test, caffeine or Priscool secretion and similar to that obtained with hydrochloric histamine.

5) The highest acid values obtained with the parenteral test appeared between 60 and 90 minutes, that is to say, in periods similar to those in the histamine test but the acid values were very much more premature than those obtained with foods by local application.

6) The test that we shall call "imidazoline or Priscool" offers a good method for examining the gastric secretion. It has the same advantages as those by histamine without determining the general or local reactions of the former.

Time in which the highest free and total acidity has been produced

No.	Minutes	Free ac.	Total ac.	No.	Minutes	Free ac.	Total ac.
1	30	19	28	16	90	47	67
2	60	105	125	17	90	0	11
3	120	115	118	18	30	21	35
4	120	0	14	19	60	42	45
5	60	91	120	20	60	45	57
6	90	15	30	21	120	38	68
7	90	70	101	22	90	6	12
8	90	30	44	23	60	25	33
9	120	28	33	24	90	20	35
10	60	55	70	25	120	38	60
11	90	0	15	26	60	34	40
12	90	43	60	27	90	15	30
13	90	0	14	28	60	48	56
14	90	75	85	29	90	38	50
15	90	18	26				

SUMMARY

Hydrochloride of 2-Bencil 4-5 imidazoline (Priscool): a new chemical compound whose stimulant action on gastric secretion has been tested as well by oral as by parenteral administration on a group of more than 70

gastrointestinal patients. The results obtained and analyzed comparatively with other classes of chemical substances, also stimulants of gastric secretion, such as alcohol or histamine, show that this substance whether applied locally or by parenteral use determines the appearance of a gastric secretion superior in quantity and quality to that obtained by Erlmann's food test or by caffeine, and very similar to that obtained by the histamine test without causing its disturbances.

A solution of 1% or 2% of this substance, in 300 cc. applied locally or in doses of 10 mg. by parenteral use, constitutes an excellent method for gastric re-

search by its easy administration as well as being harmless.

Note: The substance used by us, or say, hydrochloric of 2-Bencil 4-5 imidazoline, is a compound synthesized in Switzerland in 1939 by Hardman and Isler and registered by Ciba under the trade name of "Priscol".

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The Effectiveness of Different Culture Media in the Isolation of Enteric Microorganisms*

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IN MANY cases of enteric infection the cause of the disease can be determined by means of microbiological methods, such as cultural and serological examinations. This holds true particularly in such maladies as typhoid fever and paratyphoid infections, as well as amebic and bacillary dysentery. In other instances, however, these procedures fail to clarify the etiology of the illness. This is due in part to the fact that intestinal infections may be caused by microorganisms as yet unknown, for instance, in epidemic diarrhea of the newly-born. In other cases, bacteriological examination reveals the presence of bacteria whose pathogenic significance is by no means fully elucidated. To this group of "doubtful" pathogenic organisms belong such species as *B. proteus*, *B. pyocyaneus*, *B. morganii*, and the members of the paracolon group. Investigations carried out during the last few years indicate that these organisms may play a far greater role in infectious diarrhea than has been previously anticipated. In a subsequent paper we shall present the clinical aspects of diarrheal disease in infants and children.

Considerable advances have been made during recent years in the methods used for isolation of enteric pathogens. Three culture media seem to be particularly efficacious for this purpose. (1) Bismuth sulfite agar of Wilson and Blair for the isolation of typhoid and certain paratyphoid bacilli; (2) desoxycholate-citrate

(DC) agar; and (3) Salmonella-Shigella (SS) agar for the isolation of various enteric pathogens. Furthermore, attempts have been made to overcome the difficulty encountered in the recovery of these organisms from fecal specimens which cannot be examined immediately. It is the purpose of preserving or enriching fluids to allow for the survival of the pathogenic bacteria.

It seemed of interest to determine the usefulness of these different culture media for the isolation of pathogenic and "doubtful" pathogenic enteric organisms. The results of our investigation are presented in this paper.

MATERIAL AND METHODS

The following culture media were used: (1) Endo agar (Difco); (2) MacConkey agar (Difco); (3) desoxycholate-citrate (DC) agar (Baltimore Biological Laboratory); and (4) Salmonella-Shigella (SS) agar (Difco). In addition, the enriching fluid described by Bangxang and Eliot (1) was used. It was obtained from the Baltimore Biological Laboratory through the courtesy of Mr. T. J. Carski.

Stool specimens were streaked on one plate each of these four culture media, either directly or from broth in which a small amount of fecal material had been suspended. The method used for inoculation has been described previously (Neter (2)). In the vast majority of instances, isolated colonies were present after an incubation period of 18 to 24 hours at 37°C.

To approximately 5 cc of enriching fluid 1 to 2 loops-

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ful of fecal material were added. The tubes were shaken and then incubated at 37°C. for a period of 18 to 24 hours. Then, this suspension was used for inoculation of either Endo or MacConkey agar. It is important to test the enriching fluid for the presence of enteric organisms prior to its use. On two occasions it contained *B. pyocyaneus* and, therefore, had to be discarded.

Non-lactose fermenting colonies were fished from these different culture media and studied with respect to morphology, motility, biochemical characteristics, and antigenic structure.

RESULTS

During the period from May 19, 1943 to November 30, 1943 a total of 500 consecutive stool specimens obtained from infants and children with diarrheal disease were examined. Only aerobic, non-spore-bearing, gram-negative bacilli were identified. This report is concerned solely with organisms other than *B. coli*, *B. aerogenes*, and intermediates.

Among 500 specimens, 324 contained such species as *B. typhosus*, various members of the genus *Salmonella*, dysentery bacilli and allied organisms, *B. proteus*, *B. pyocyaneus*, *B. alcaligenes*, *B. morganii* type I, and a group of bacteria tentatively identified as paracolon bacilli. Tables 1 to 6 present the results obtained in the

TABLE 1

Isolation of Eberthella from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding <i>Eberthella</i>	1	2	1	1	1
Total number of specimens examined	2	2	2	2	2

isolation of these microorganisms from the various culture media employed, namely, Endo, MacConkey, *Salmonella-Shigella* (SS), desoxycholate-citrate (DC) agar, and enriching fluid.

Only two specimens contained *B. typhosus* (Table 1). No conclusions, therefore, can be drawn with respect to the usefulness of the different culture media in the isolation of this organism.

As may be seen from Table 2, members of the genus *Salmonella* were present in 29 stool specimens. The following species were encountered: *S. paratyphi* B, *S. typhi* murium, and *S. thompson*. It is evident that in this series Endo agar yielded the least and SS agar the

TABLE 2

Isolation of Salmonella from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding <i>Salmonella</i>	5	13	15	9	12
Total number of specimens examined	28	29	29	27	27

most satisfactory results. MacConkey agar proved to be somewhat superior to DC agar and was approximately as effective as enriching fluid. It is important to emphasize that no single culture medium allowed for the isolation of paratyphoid bacilli from all positive specimens. Thus, several culture media should be employed simultaneously.

Table 3 presents the results obtained with respect to dysentery bacilli and allied species. Out of a total of 500 fecal specimens, 50 (10%) contained these organisms. The table indicates that SS and DC agar were definitely superior to Endo agar, MacConkey agar, and enriching fluid. Again, from no single culture medium were these organisms isolated from all positive specimens.

B. proteus was encountered in 40 out of 500 fecal specimens (Table 4). It is particularly worthy of note that this organism was recovered from a greater number of specimens by the use of Endo agar, MacConkey

TABLE 3

Isolation of Shigella from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding <i>Shigella</i>	13	23	32	34	23
Total number of specimens examined	50	50	49	50	48

agar, and enriching fluid than from SS and DC agar. In all probability, this is due to the fact that, in contradistinction to Endo agar, SS and DC agar prevent or inhibit the spread of *B. proteus* or its growth.

Of special interest is the large number of stool specimens containing *B. morganii* type I and paracolon bacilli. As may be seen from Table 5, out of a total of 500 stool samples no fewer than 207 contained these organisms. SS and DC agar were definitely superior to Endo and MacConkey agar, while the results obtained with enriching fluid stand midway between these two groups. The significance of these organisms in diarrheal disease will be discussed in a subsequent paper. It suffices to mention here that this group of microorganisms may not be the primary cause of the malady; rather, it is possible that they are normal inhabitants of the intestinal tract becoming more predominant under abnormal conditions.

TABLE 4

Isolation of Proteus from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding <i>Proteus</i>	22	23	18	17	24
Total number of specimens examined	40	39	39	39	37

With a group of miscellaneous organisms, namely, *B. alcaligenes*, *B. pyocyaneus*, and *B. coli* anaerogenes, SS and DC agar as well as enriching fluid proved to be more efficacious than Endo and MacConkey agar (Table 6).

In the majority of stool examinations the organisms under consideration were recovered from several culture media. In 73 out of 217 positive specimens, however, these bacteria were isolated from only one culture medium (Table 7). From this table it is worth noting that from 31 stool samples these microorganisms were isolated solely by the use of enriching fluid. It is suggested, therefore, that this particular medium be used routinely in the bacteriological examination of feces.

It is well known that both SS and DC agar more or less inhibit the growth of the normal intestinal gram-negative bacilli. The question arises as to how often

no growth of any organisms, including enteric pathogens, occurs. Incubation of enriching fluid, too, results in a decrease in the number of coliform organisms. It seemed of interest, therefore, to tabulate the number of stool specimens which yielded no growth of any organism on the different culture media employed. The results are presented in Table 8. It may be seen that a total of 49 stool specimens failed to show growth on one culture medium. It is also evident that this occurred more often with SS and DC agar than with enriching fluid and least often with Endo and MacConkey agar.

TABLE 5

Isolation of Morgan type I and paracolon bacilli from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding Morgan and paracolon bacilli	71	119	165	153	139
Total number of specimens examined	207	205	205	205	197

Aside from *B. coli*, *B. aerogenes*, and intermediates, mixed cultures of aerobic, non-spore-bearing, gram-negative bacilli were obtained with 26 stool specimens (Table 9). It seems very likely that the percentage of mixed cultures would have been higher if more non-lactose fermenting colonies had been isolated.

It is well known that the presence of *B. proteus* may interfere with the isolation of other non-lactose fermenting colonies. As may be seen from Table 10, SS and DC agar are distinctly superior to Endo and MacConkey agar inasmuch as they allowed the isolation of *Salmonella*, *Shigella*, and other non-lactose fermenting bacilli in the presence of *B. proteus* from a greater number of specimens. This table shows, furthermore, that the use of enriching fluid, too, resulted in the isolation of more enteric pathogens than were recovered from Endo agar. However, enriching fluid proved to be less efficacious than SS and DC agar.

DISCUSSION

During the last few years definite strides forward have been made in the isolation of enteric pathogens. It is now possible to isolate in a greater percentage of

TABLE 6

Isolation of miscellaneous organisms from positive stool specimens

	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid
Number of specimens yielding miscellaneous organisms	4	8	13	11	13
Total number of specimens examined	21	22	21	22	22

cases the causative agent from the feces, such as paratyphoid and dysentery bacilli. Two culture media in particular have been proven to be useful for this purpose, namely desoxycholate-citrate (DC) and *Shigella-Salmonella* (SS) agar. The former medium was introduced in 1935 by Leifson (3). Its usefulness was confirmed by several authors, including Paulson (4), Hardy, Watt, DeCapito, and Kolodny (5). Cooper,

Furcolow, Mitchell, and Cullen (6), Irons, Bohles, De Shazo, and Hewlett (7), Coleman (8), Mayfield and Gober (9, 10), Hormaeche and Surraco (11). The suitability of the SS medium for the isolation of dysentery bacilli was established by Mayfield and Gober (10), Hormaeche and Surraco (11), Hardy, Watt, DeCapito, and Kolodny (5), Hardy, Watt, and DeCapito (12), Pot (13), Rose and Kolodny (14), Kulins (15), as well as Mollov, Winter, and Steinberg (16).

The above reported investigations confirm and extend these findings, namely, that DC and SS agar are definitely superior to Endo and MacConkey agar in the isolation of certain intestinal microorganisms. For instance, dysentery bacilli could be isolated from 50 positive stool specimens, in 13 instances from Endo agar, in 23 from MacConkey agar, in 32 from SS agar, and in 34 from DC agar. In the case of paratyphoid bacilli, SS agar proved to be the best culture medium in this series. On the other hand, it is important to emphasize that none of the culture media used alone allowed for the isolation of these organisms from all positive specimens. Moreover, in 73 instances the respective microorganisms were isolated from only one of the four culture media used. Isolation of organisms such as *Salmonella*, *Shigella*, *Morgan bacillus* type I, etc., was possible from Endo agar exclusively in four instances, from MacConkey in seven, from DC in eleven, and from SS agar in twenty. Finally, it should

TABLE 7

Number of successful isolations from only one out of five culture media used

Strain isolated	Endo agar	MacConkey agar	SS agar	Desoxycholate-citrate agar	Enriching fluid	
Eberthella	0	0	0	0	0	
Salmonella	0	3	5	1	5	
Shigella	0	1	2	6	4	
Morgan type I and paracolon bacilli	1	3	10	2	15	
Proteus	2	0	1	0	4	
Miscellaneous organisms	1	0	2	2	3	
Total	73	4	7	20	11	31

be emphasized that even when the same technique is used, one of the culture media may fail to show any growth whatsoever. For these reasons the best results are obtained by the simultaneous use of several culture media.

It is well known that stool specimens should be examined as soon as possible. A lapse of several hours may suffice to make recovery of intestinal pathogens difficult or even impossible. To surmount this obstacle preserving and enriching fluids can be used with a two-fold purpose. Such a fluid should (1) preserve the intestinal pathogens and (2) eliminate as far as possible coliform bacilli. In the investigation reported here the enriching fluid of Bangxang and Eliot (1) has been studied. This enriching fluid is a buffered solution of sodium chloride (pH of 8.5) containing 1 percent sodium desoxycholate. Its efficacy has been shown by Felsenfeld (17). This enriching fluid proved to be superior to Endo agar in the isolation of paratyphoid and dysentery bacilli. However, with the technique employed it proved to be less effective than SS and DC agar in the isolation of *Shigella* organisms. The enriching fluid, however, allowed the isolation of paratyphoid,

dysentery, Morgan bacilli, and others in 31 out of 73 instances in which these organisms were not obtained from any other culture medium. It is our impression, therefore, that the enriching fluid should be used in conjunction with the other culture media, but it seems to be inadvisable to employ it exclusively.

In the original article of Leifson (3), it was stated that *B. morganii* is completely inhibited on DC agar. Irons and associates (7) reported that this microorganism either fails to grow on this culture medium or forms very small colorless colonies. In the above reported investigation a large number of strains of *B.*

TABLE 8

Number of stool examinations in which no growth of any microorganisms occurred

Strain isolated from other media	Endo agar	MacConkey agar	SS agar	Deoxycholate-citrate agar	Enriching fluid
<i>Eberthella</i>	0	0	1	1	0
<i>Salmonella</i>	0	0	1	0	0
<i>Shigella</i>	0	0	0	1	0
Morgan type I and paracolon bacilli	0	0	2	1	2
<i>Proteus</i>	0	0	0	0	0
Miscellaneous organisms	0	0	2	2	2
<i>B. coli</i> only	2	1	10	10	1
Total	42	2	16	17	11

morganii type I were isolated from DC agar. It is correct that the colonies of this culture medium are very small and can be readily confused with enterococci if compared to the size of colonies on Endo agar. In this connection it may be mentioned that, contrary to the statement of Leifson (3), certain strains of *B. alkalescens* grow on this agar. Therefore, this culture medium cannot be used for the differentiation of *B. alkalescens* from the closely related Flexner dysentery bacilli.

The high incidence of Morgan bacillus type I and paracolon bacilli deserves brief comment. The fact that these organisms were obtained from the stools of children and infants with diarrheal disease in 207 out of 500 specimens should not be construed to imply that these organisms were the causative agent of the malady. The high incidence of these organisms is, in all probability, due to the fact that more effective culture media have been used in this investigation. It is desirable,

TABLE 9

Mixed cultures among 500 stool specimens

Species	Number of specimens
<i>Proteus</i> and Morgan type I or paracolon bacilli	18
<i>Proteus</i> and <i>Eberthella</i>	0
<i>Proteus</i> and <i>Salmonella</i>	0
<i>Proteus</i> and <i>Shigella</i>	4
<i>Salmonella</i> and paracolon bacilli	2
<i>Salmonella</i> and <i>pyocyaneus</i>	1
Different paracolon bacilli	1
Total	26

therefore, to carry out a similar study on feces from children and infants without evidence or history of diarrheal disease. Although some evidence is at hand incriminating these organisms as enteric pathogens, no final proof is available. Moreover, until recently this group of microorganisms was not adequately investigated. Stuart and his associates (18) have carried out a most important investigation on paracolon bacilli, particularly with respect to their biochemical charac-

teristics, antigenic structure, and pathogenic significance.

Littman (19) and Fel-enfeld (20) have recently published excellent outlines for the isolation and identification of enteric bacteria. Littman recommends the use of buffered glycerine-saline solution, bile-glycerin-peptone broth, as well as deoxycholate agar, deoxycholate-citrate or *Shigella-Salmonella* agar for cultivation. The usefulness of Selenite-F broth has not been investigated here.

From the above reported investigation it may be concluded that the simultaneous use of several culture media gives superior results to any one culture medium employed in the isolation of enteric pathogens and "doubtful" enteric pathogens.

SUMMARY AND CONCLUSIONS

An investigation was carried out concerning the usefulness of various culture media in the isolation of enteric pathogens from feces of children and infants with diarrheal disease. The following results were obtained:

(1) Among 500 consecutive stool specimens 324 contained organisms other than *B. coli*, *B. aerogenes*, and intermediates. The following species were encountered: *B. typhosus*, *B. paratyphica* (Flexner), *B. schmitzii*, *B. castellanii*, *B. paratyphi* B, *B. typhi murium*, *B. thompson*, *B. proteus*, *B. morganii* type I,

TABLE 10

Isolation of mixed cultures from stool specimens containing *B. proteus*

Species	Endo agar	MacConkey agar	SS agar	Deoxycholate-citrate agar	Enriching fluid
<i>Proteus</i>	14	12	4	5	10
Other organisms (<i>Salmonella</i> , <i>Shigella</i> , etc.)	5	8	13	14	0

paracolon bacilli, *B. pyocyaneus*, *B. alcaligenes*, and *B. coli* anaerogenes.

(2) Among the culture media used *Shigella-Salmonella* and deoxycholate-citrate agar proved to be superior to enriching fluid, and enriching fluid superior to Endo and MacConkey agar in the isolation of these organisms.

(3) *B. morganii* and paracolon bacilli were present in 207 out of 500 specimens.

(4) Twenty-six specimens, aside from *B. coli*, *B. aerogenes*, and intermediates, contained more than one species of aerobic, non-spore-bearing, gram-negative bacilli.

(5) In the presence of *B. proteus* these organisms are more readily recovered from SS and DC agar than from Endo and MacConkey agar.

(6) Isolation of any of these organisms from only one out of five culture media was accomplished in seventy-three instances. Enriching fluid proved to be more valuable than SS and DC agar and these latter better than MacConkey and Endo agar in these cases.

(7) It is concluded that no single culture medium allows for the optimal isolation of these organisms and that the simultaneous use of several culture media yields the best results.

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WARREN TAYLOR VAUGHAN, M. D.

Obituary

On April 12, 1944, Dr. Warren Taylor Vaughan, internationally known authority on allergy, died suddenly of coronary occlusion at his home in Richmond, Virginia, at the age of 51.

Dr. Vaughan's contributions to the field of allergy were significant, and his interest in allied fields of medicine is manifested in the diversity of recognition accorded him. He was one of two members of the Section on Allergy of the Editorial Council of the *American Journal of Digestive Diseases*, a member of the editorial board of the *Review of Gastroenterology* and of the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases*, collaborating editor of the *American Journal of Clinical Pathology*, editor-in-chief of the *Journal of Laboratory and Clinical Medicine*, and prior to January 1944, was associate editor of the *Journal of Allergy*. His contributions to foreign journals were many, and he was collaborating editor of "*Folie Clinica Chimica Microscopia*" (Bologna, Italy).

Among Dr. Vaughan's most important contributions to the field of allergy was his study of the manifestations of food allergy, which required a broad knowledge of the pathology of the gastro-intestinal tract as well as of less frequently acknowledged manifestation of food allergy such as rhinitis, atopic dermatitis, asthma, migraine, and others. About 1929 Dr. Vaughan undertook the botanical classification of foods in groups in the belief that the crossed allergenic reactions to foods were similar to those previously found to pollens. His theory based on a knowledge of the biologic kinship of foods,

that the proper grouping of chemically related allergens in a single endermal test might give positive reaction when the reaction to individual allergens was apparently negative, enabled the circumvention of some of the false negative skin reactions through a study of the response to ingestion of negative members of a positive group. This theory was successful in individual cases. In selected cases his leukopenic index has proved to be another satisfactory laboratory method of diagnosing food allergy. His index of the incidence of allergy has become a generally accepted standard.

A fitting monument to the ability of this untiring and progressive clinician exists in the large number of physicians and technicians trained at his clinic in the specialty of allergy who have looked to Dr. Vaughan for guidance in all phases of this work. His textbooks and his many other publications will give to future allergists an appreciation of the importance of his work in their particular field of science.

Dr. Vaughan's father was the late Dr. Victor C. Vaughan, Dean of the Medical School of the University of Michigan from 1891 to 1921, and a former president of the American Medical Association, and well known in the field of immunology. Dr. Vaughan is survived by his wife, the former Emma Elizabeth Heath, and four sons, Warren T., Jr., and Victor III, both of whom are physicians, and John and David who are students at Harvard Medical School.

J. WARRICK THOMAS, M.D.,
Cleveland, Ohio.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

BERSACK, S. R.: *Carcinoma of the esophagus in association with achalasia of the cardia.* (*Radiol.*, V, 42, P. 220, March, 1944.)

Achalasia is preferred to cardiospasm as a term describing failure of the cardia to relax due to functional disturbances. Where gross anatomical disturbances of the cardia exist, the term cardiospasm might be retained. Of 227 patients with carcinoma of the esophagus admitted to hospital, only one had an associated achalasia of the cardia. No special changes in symptoms are noted when the carcinoma occurs high up in the esophagus. Even in late stages often no obstruction to the passage of food is found. Emphasis is placed on evacuation of the esophagus of its retained contents before radiologic examination is made.—I. M. Theone.

BOWEL

SMITH, L. A., GOOD, C. A. AND CROY, H. K.: *Tumor of the small intestine as the cause of recurrent melena: report of two cases.* (*Proceed. Staff Meet. Mayo Clinic.*, V, 19, P. 117, March 18, 1944.)

There are three possible explanations for recurrent bleeding by the bowel after surgical intervention for ulcer. The bleeding may occur as a postoperative complication in association with the lesion of the original ulcer, it may be the result of a new lesion unrelated to the original ulcer, or it may be the result of a lesion which existed prior to operation but was not recognized. Many structural lesions may give rise to tarry stools but the commonest are gastric carcinoma and peptic ulcer. The incidence of bleeding among tumors of the ileum or jejunum is high. Hematemesis may occur from tumors of the duodenum but usually melena alone occurs.

Two cases of duodenal lesion with coexisting tumor of the jejunum or ileum are presented. Symptoms were those of peptic ulcer. Operation for ulcer did not stop the melena. At subsequent reoperation one case revealed a tumor in the terminal jejunum whilst the other a tumor in the mid-portion of the ileum.

In discussing the paper, Dr. Good points out that 266 potential sources of bleeding were found in the stomach and duodenum (gastric carcinoma and peptic ulcer) for each one found in the small intestine beyond the duodenal bulb. Dr. Gray estimates that 95 per cent

of cases of melena, hematemesis, or both, occur from lesions in the stomach or duodenum. Approximately 40 per cent of the hemorrhages originate in duodenal ulcer, 20 per cent in gastric carcinoma, 18 per cent in gastric ulcer, 5 per cent in oesophageal varices and the remainder in lesions elsewhere.—F. N. Chockley.

ROSENBLATT, M. S.: *Duodenal obstruction and stasis.* (*Western J. Surg. Obstet. Gynec.*, V, 52, P. 69, Feb., 1944.)

Various causes of duodenal obstruction and stasis are outlined and the suggestion is made that accentuation of the normal angle at the duodenal-jejunal junction may be a contributing cause. In cases due to failure of bowel rotation, the Todd operation is best. In cases due to obstruction of the mesenteric vessels, the operative procedure of choice is duodenojejunostomy. Freeing of the ligament of Treitz in order to lower the duodenal-jejunal angle is advocated for selected cases. In all adult cases, medical treatment should be tried before resorting to surgery.—I. M. Theone.

ARNEDO, C. F.: *Pathologic anatomy of intestinal tuberculosis.* (*Rev. Med. Rosario*, V, 33, P. 764, 1943.)

Intestinal tuberculosis is a primary problem in tuberculosis control, due to both its incidence and malignity. Factors in its decreasing occurrence are early recognition of pulmonary tuberculosis, a better appreciation of the occurrence of intestinal complications, and progress in therapy, particularly with respect to diet. Despite these factors, 71.9 per cent of 600 tuberculous patients showed intestinal tuberculosis at necropsy. Clinically, there are 4 types: acute, in 20 per cent; subacute, in 14 per cent; chronic, in 27 per cent; and exacerbations of the chronic type, in 10 per cent. In 14 per cent, the lesions were minimal; in 19 per cent, moderate; and in 38 per cent, generalized. The severity of intestinal infections parallels that of pulmonary tuberculosis. In 23.8 per cent, the lesions were localized in the jejunal-ileal region, and in 11.9 per cent, in the ascending colon. Surgical and medical measures in treatment are discussed.—Courtesy Biological Abstracts.

D'OIDIO, F. R., J. BELLINGI, AND H. MATURI: *Severe hemorrhagic tuberculous enteritis.* (*Rev. Med. Rosario*, V, 33, P. 801, 1943.)

Clinical and necropsy studies of 3 cases of severe hemorrhagic tuberculous enteritis are presented.—Biological Abstracts..

NUNEZ, CALIZTO, J.: *Intestinal tuberculosis*. (Rev. Med. Rosario, V. 33, P. 738, 1943.)

Clinical aspects of intestinal tuberculosis are extensively reviewed, with 41 references.—Courtesy Biological Abstracts.

AHUMADA, J. C., AND RAUL M. CHEVALIER.: *Actinogenitic rectopathies*. (Rev. Assoc. Med. Argentina, V. 57, P. 86, 1943.)

Twenty cases with rectal lesions following radium therapy of the uterus are summarized. Three grades were noted: minimal lesions of the mucosa evidenced by telangiectasis and moderate pain; single ulcers with moderate clinical symptoms; and fistulation, with intense rectalgia fever, emaciation and discharge of feces through the vagina. Incidence of these three grades were 2, 12, and 6 respectively. Diagnosis and treatment are discussed.—Courtesy Biological Abstracts.

SAKULA, J.: *Outbreak of gastroenteritis in newborn*. (Lancet, V. 2, P. 758, Dec. 18, 1943.)

In November, 1942 an outbreak of gastro-enteritis of the newborn occurred in the maternity department of the Central Middlesex County Hospital. As a rule the onset was sudden with the first symptom usually an unexplained vomiting. In a few cases the first symptom was a sudden loss in weight in children otherwise apparently well. The stools averaged 6 to 7 per day. The length of illness varied from 2 to 21 days, and averaged just over 7 days. The temperature was usually either normal or raised to about 100°F. Progress, if any, was slow, and death was often sudden. Of a possible 31 children, 18 became ill and 15 died, giving a case-mortality rate of 83%. Of the 15 children who died 13 had fairly full autopsies. The findings did not indicate an acute intestinal infection,—or even a septicaemia,—but probably a toxic condition which caused wasting of the thymus and suprarenals and degeneration in the liver. Bacteriological examination showed the streptococcal distribution to be normal in the intestine. *Pseudomonas pyocyanca* was isolated in half the cases. However this was not considered sufficient to show the organism to be the primary cause of the infection. As to treatment, the chief aims should be to guard against dehydration and to protect the liver. The outbreak was confined to bottle-fed infants. To prevent such outbreaks, breast-feeding should be encouraged, and in infant nurseries special precautions should be taken to avoid infection through bottle feeds.—George P. Blundell.

KAISER, I. H.: *Rectal stricture complicating labor*. (Am. J. Obst. Gyn., V. 46, P. 672, November, 1943)

This paper is based on a study of 48 cases from the Obstetric service of Johns Hopkins Hospital. This survey was undertaken since there appeared to be rather a scarcity of such reported cases in literature. Stricture of the rectum may be the result of lympho-

pathia venereum, syphilis, tuberculosis, and other rarer causes. Estimation of the importance of stricture as a cause of dystocia depends upon careful examination and description, not only of the caliber of the stricture, but also of the status of the recto-vaginal septum, of the location of the stricture, of the consistency of the scar tissue, and of its extent in the connective tissue of the pelvis.

A program is recommended by the author where consideration is given to the individual patient. A special emphasis is placed on the following, for patients in labor, location and extent of the rectal scarring. Caesarian section is reserved for those patients with extensive involvement of the pouch of Douglas or the pelvic soft parts. Colostomy or precolostomy may be performed in association with Caesarian section if necessary. A pre-existing colostomy is not a contra-indication to pelvic delivery, and excessive sedation is to be avoided. It is advisable to observe the patient carefully post-partum for evidence pointing to rupture of the rectum.

In the 30 cases collected from the literature, it was emphasized that they were isolated cases. In this group, there were 7 fatalities for a total of 23%, while in the cases of Johns Hopkins Hospital, rupture of the rectum occurred in only one case. In their series, there occurred one death due to rupture of the uterus which apparently had no connection with rectal stricture.—J. B. Bernstine.

RUNNING, E. H.: *Vomiting during first days of life*. (Southwest Med., V. 27, P. 274, Nov., 1943.)

Severe vomiting during the first few days of life requires an early and accurate diagnosis before the harmful results occur, viz: severe dehydration, acidosis, or alkalosis. The causation of this vomiting can be due to a variety of factors. During the first few hours of life, it is usually associated with mucus in excess in the upper respiratory tract. Simple aspiration and careful watching suffice as treatment. Should cyanosis occur and continue with other evidences of disturbed circulation or convulsive movements, cerebral hemorrhage should be suspected, although vomiting is not the main sign or symptom of this condition.

After the first twelve to twenty-four hours, when water or betalactose solution is usually given and severe vomiting occurs, then congenital defects should be suspected; such as, atresia of the esophagus, esophageal-respiratory communication, and duodenal obstruction. These are diagnosed by catheterization plus x-ray, and the administration of barium plus x-ray. Pyloric obstruction is rarely diagnosed during the first week.

Of importance is the type of vomiting caused by functional factors. It usually occurs between the second and fourth day and is characterized by the reflux of bile. It is usually accompanied by somnolence and persists for a few days, rarely a week. Perhaps it is due to pressure on the brain and is akin to vomiting that accompanies brain concussion at any time. It occurs equally in the breast or bottle-fed baby and calls for no changing in the feeding regimen. It is for this type of vomiting that the author offers a form of treat-

ment. He lavages the stomach with warm water or salt solution and cleanses it of the bile-stained mucus which is of a gummy consistency. This one lavage continued until the returns are clear is usually enough to relieve the patient, but it is wise to lavage before each feeding until the vomiting has stopped. This technique should be instituted in all cases of severe vomiting, especially those associated with somnolence and failure to nurse.—J. B. Bernstein.

BARGEN, J. A.: *The present status of ulcerative colitis and regional enteritis.* (Bull. New York Acad. Med., V. 20, P. 34, Jan., 1944.)

The term "chronic ulcerative colitis" and "regional enteritis" should be reserved to designate general clinico-pathological syndromes rather than disease entities. The etiologic type should guide the study of these syndromes for best results in therapy. Each type has a feature which makes it distinctive and differentiates it from other types. Barga divides intestinal lesions into three main groups, namely those chiefly involving the small intestine, those chiefly involving the large intestine, and those involving both small and large intestine by spreading. Involving the large intestines are streptococcal ulcerative colitis, amoebic ulcerative colitis, ulcerative colitis of venereal lymphogranuloma, and a regional ulcerative colitis of unknown etiology. Involving the small intestine are ulcerative intestinal tuberculosis and the so-called regional ileitis. Lesions involving the whole intestine are chronic bacillary dysentery, allergic colitis, ulcerative ileocolitis of unknown etiology, and a deficiency syndrome. The diffuseness of the lesion, the proctoscopic and roentgenologic findings, the history, and the type of organism which may be recovered, are important in formulating the diagnosis. The agglutinin titer in cases of *Shigella dysenteriae* and the positive Frei reaction in cases of venereal lymphogranuloma are significant.—G. Klenner.

PANCREAS

PASTERNAK, J. G.: *Calcareous pancreatitis; report of three cases with autopsies.* (Ann. Int. Med., V. 19, P. 757, 1943.)

In only about half of the cases of calcareous pancreatitis are there signs and symptoms of pancreatic insufficiency. Bulky pale stools, inanition, and extreme asthenia are characteristic. Calcareous deposits are shown by roentgenological examination of the pancreas.

The etiology is unknown. Infection via ducts may be a factor. Other factors suspected are regurgitation from the biliary tree and stasis of pancreatic secretions. Once formed, the calcification about the primary calcareous focus proceeds. The concretions may be either incrustated in the duct wall or lie free in the duct lumen. The calculi and calcareous deposits ultimately lead to atrophy and progressive fibrosis. The destruction of the gland tissue is variable and depends on the extent of the calcareous deposition. The first cells affected are the acini, only in the late stages of the disease are the islet cells involved.—G. Klenner.

LIONELLO, J., FICARRA, B. J., AND RYAN, N. H.: *Pancreatic calculi, report of seven cases in two of which cure was effected by pancreaticolithotomy.* (Arch. Surg., V. 48, P. 137, February, 1944.)

The exact number of cases of pancreatic lithiasis which have been reported in the literature is uncertain, but the incidence is low. The authors have collected a total of 232 cases. There is no typical clinical picture so that diagnosis by signs and symptoms is difficult. The reflex disturbances of digestion are dependent on the extent of the involvement. Sometimes the condition is almost asymptomatic. Laboratory findings are not of great aid but roentgenograms may be very helpful. The stones are radio-opaque because of the high calcium carbonate content; fluoroscopy does not reveal their position.

Surgical intervention is indicated once the diagnosis is made. Approached through the gastrocolic omentum, the operative mortality is 7 per cent. Unless removed, the calculi may lead to destruction of the pancreas.—

F. N. Chockly.

LIVER AND GALL BLADDER

KRISE, HERNAN A.: *Biliary tract syndrome.* (Rev. Med. Rosario, V. 33, P. 491, 1943.)

Clinical aspects of the disease of the bile ducts are fully discussed, with emphasis on diagnosis. Four types are figured. Results of duodenal catheterization are positive in choledocholithiasis with incomplete obstruction; completely negative in neoplasms of the terminal portion of the common bile duct, or choledochopancreatic cancer; negative in neoplasms of the smaller biliary ducts with complete obstruction, but positive for pancreatic enzymes in contrast to the latter; and variable in cancer of the ampule of Vater, since the block may be intermittent or complete, and frequently blood or neoplastic cells are found. Some 70 references are cited.—Courtesy Biological Abstracts.

CONSTAM, CHARLOTTE: *True atrophic liver cirrhoses.* (Helvetica Medica Acta, V. 10, P. 507, 1943.)

In 1,423 autopsies performed between January, 1937 and July, 1940, cirrhosis of the liver was observed in 160 cases, of which 150 represented true atrophic cirrhosis (Laennec). Only in 12 of these 150 cases the history did not reveal alcoholic abuse. About half of the cirrhoses were discovered only at autopsy. Diabetes mellitus existed in 11 per cent, diseases of the bile bladder or ducts in 20 per cent, and active tuberculosis in 17 per cent of the cirrhosis patients. Only in 15 per cent was the cirrhosis the primary factor for death.—Courtesy Biological Abstracts.

RENNIE, J. B.: *Hippuric acid synthesis as a test of hepatic efficiency.* (Brit. Jour. Exp. Path., V. 23, P. 329, 1942.)

The author studied the synthesis of hippuric acid from sodium benzoate in a large number of normal persons and in many individuals with various well defined clinical conditions. Sixty-nine normals were studied and the amounts of hippuric acid excreted in

4 hours varied from 2.4 to 4.39 grams, the mean value being 3.19 with a standard deviation of 1.07 grams. In 64 observations on 17 cases of acute epidemic hepatitis (? etiology) the values were below 2.4 in all cases except 3. Hippuric acid synthesis was uniformly low in 5 cases of acute hepatitis, 13 cases of secondary carcinoma of the liver, 12 or 13 cases of cirrhosis of the liver and 8 or 9 cases of obstructive jaundice. The results of similar tests in cases of cholecystitis were variable.—Courtesy Biological Abstracts.

WILLIS, R. A.: *Carcinoma arising in congenital cysts of the liver.* (*J. Path. Bact.*, V. 55, P. 492, 1943.)

Multiple developmental cysts of the epithelial lining of the liver gave rise in a woman aged 27 years to a diffuse carcinoma. The malignancy extended into the liver itself and also was found in the lungs and lymph glands. The tumor cells are described as having unusual types of mitotic figures.—G. Klenner.

THERAPEUTICS

KLEWITZ, FELIX: *Is alkali therapy in gastric and duodenal ulcer justified?* (*Deutsch. med. Wochenschr.*, V. 67, P. 1070, 1941.)

The mode of action of alkali therapy in gastric and duodenal ulcers is discussed in relation to systemic changes in acid-base equilibrium. The urines of 81 healthy persons 2 hours after ingestion of 5 grams sodium bicarbonate in the morning were at pH 8; those of 49 ulcer patients similarly treated never showed a pH greater than 7.6.—Courtesy Biological Abstracts.

GOUGH, N.: *Concentration of sulfapyridine in bile.* (*Lancet*, V. 2, P. 571, Nov. 6, 1943.)

An initial dose of 2 grams of sulfapyridine followed by a maintenance dose of 1 gram administered orally every four hours was given to eight patients on whom a biliary fistula had been performed. Bile and blood samples were collected every six hours for two days. In all of the eight cases the maximal level of the drug in the bile (6 to 8 mg. per 100 ml) was higher than in the blood (3 to 4 mg. per 100 ml). On two patients given one gram of the drug every four hours for twenty-four hours prior to cholecystectomy, the values obtained in one case were 8 mg. per 100 ml for common duct bile, 11.7 for gallbladder bile, and blood concentration of 4.5 mg. per 100 ml of the free drug. In the second case, reported as a non-functioning gallbladder, values of 13.2, 12.9, and 3.1 mg. per 100 ml were obtained.

The author concludes that sulfapyridine, despite the adverse effects on secretory and concentrating power of the liver and gallbladder which accompany pathological changes in these organs, may reach a concentration in the bile, which in the blood would be effective against certain organisms.—H. Siplet.

BRANCO RIBEIRO, E.: *Drainage of ductus choledocus.* (*Bol. Sanatorio Sao Lucas*, V. 4, P. 179, 1943.)

The description is given of a non-surgical method of removing gall stones from the bile duct by dissolving

them with injection of alcohol and ether mixtures.—Courtesy Biological Abstracts.

SURGERY

JUDD, D. B., CLAGETT, O. T., HAVENS, F. Z., AND MOERSCH, H. J.: *Tracheo-oesophageal fistula; report of case.* (*Proc. Staff Meet. Mayo Clinic*, V. 19, P. 100, Feb. 23, 1944.)

This uncommon pathologic condition gives rise to very distressing symptoms, chiefly respiratory, associated with dysphagia. Death results from pulmonary or mediastinal infection. Surgical repair has been seldom attempted because in the past the chances of success have been slight.

The case is presented of a man in whom a bullet passed through the thyroid gland, thyroid cartilage, trachea, oesophagus, and soft tissues of the shoulder. Both recurrent laryngeal arteries were severed. After emergency measures to control bleeding were carried out, the patient was fed through a gastrostomy. Later the oesophagus was closed and the closure reinforced by a pedicle muscle flap from the sternocleidomastoid muscle. Bilateral submucous resection of the vocal cords was also done to assure an adequate airway.—D. A. Wocker.

RUSSO, ARMANDO G.: *Exploration of the ductus choledocus during operation.* (*Rev. Assoc. Med. Argentina*, V. 57, P. 505, 1943.)

Technics of exploring the bile ducts are discussed with two case reports of failure to find obstructions diagnosed on clinical grounds. Roentgenograms are presented in these two cases.—Courtesy Biological Abstracts.

EXPERIMENTAL MEDICINE

SECRETION

GROSSMAN, M. I., GREENGARD, H., IVY, A. C.: *On the mechanism of the adaptation of pancreatic enzymes to dietary composition.* (*Am. J. Phys.*, V. 141, P. 38, Jan., 1944.)

Rats on a constant diet show adaptations of amylase and trypsin content of pancreatic juice when the carbohydrate or protein intake is increased. Three explanations of this mechanism are possible, (1) reflex secretory, (2) hormone, (3) products of digestion. The character of the stimulus (i.e., undigested, partly digested, completely digested food) must also be considered.

Dextrose (replacing corn starch) diets increased amylase and lipase but not trypsin. Casein hydrolysate (replacing casein) decreased trypsin content but did not change lipase or amylase. Daily subcutaneous injections of protamine zinc insulin depressed amylase, the other enzymes remaining unchanged.

From these experiments it seems that the products of carbohydrate digestion excite an increase in amylase while protein hydrolysates do not increase trypsin. This suggests a humoral mechanism for dextrose and a reflex factor for trypsin regulation. However, since the protein hydrolysate contained only amino acids and

polypeptids, a more complex hydrolytic product of protein digestion (such as proteose) may be the stimulus.

These effects are not due to any known factors controlling enzyme secretion which act rapidly and influence all enzymes in a parallel manner. Adaptation to diet involves selective increases in enzyme output and require a long period of time.—M. J. Oppenheimer.

MOTILITY

YOUNG, W. B., KARSTENS, A. I., AND GRISWOLD, H. E., JR.: *Action of anti-cholinesterases on the motility of the extrinsically denervated intestine in situ.* (*J. Pharmacol. Exper. Therap.*, V. 80, P. 205, March, 1944.)

Intestinal motility was studied by the balloon method, using unanesthetized dogs with Thiry fistulas of the jejunum. The extrinsic nerve supply to these loops had been interrupted surgically, so that the intestino-intestinal reflexes and pain responses to pressure in the loop were absent.

Prostigmin and physostigmin exerted their characteristic excitatory action on the motility of the denervated intestine and this action was prevented or reduced by atropine. The minimal dose of the anti-cholinesterases is sufficient to potentiate the excitatory action of acetylcholine while the minimal dose of atropine is sufficient to reduce the excitatory action of the acetylcholine.

The action of the physostigmin and prostigmin are the same on the denervated intestine as on the innervated intestine. The results may be explained by postulating that these drugs have a direct excitatory action on the intestinal motility exclusive of their anti-cholinesterase action. On the other hand, they may be explained by assuming that the drugs act to prevent acetylcholine destruction by choline esterase and that the acetylcholine in the denervated muscle is either formed by the intrinsic nervous mechanism or brought there by the blood stream.—M. H. F. Friedman.

PHARMACOLOGY

DEICHMANN, H., AND WITHERUP, S.: *Observations on the ingestion of methyl cellulose and ethyl cellulose by rats.* (*J. Lab. Clin. Med.*, V. 28, P. 1725, November, 1943.)

The possible deleterious effects of methyl cellulose and ethyl cellulose because of their potential usefulness as thickening and binding agents in the pharmaceutical and food industries were investigated.

Methyl cellulose incorporated in the food and drinking water of 80 rats with a daily ingestion of about 0.44 gms. per rat and ethyl cellulose of about 0.18 gm. per rat daily in the food only, fed over a period of eight months, showed no significant difference in the weight and growth of these animals against a corresponding number of control animals. There was likewise no evidence of significant gross or microscopic abnormalities in the tissues of these animals.

It is concluded that the feeding of methyl and ethyl cellulose in these concentrations is harmless to rats.—H. Sipler.

PATHOLOGY

GUNN, C. K.: *Hereditary acholuric jaundice in the rat.* (*Canad. Med. Assoc. J.*, V. 50, P. 230, March, 1944.)

There appears to be no record of hereditary jaundice among animals other than man. In 1934 a mutant strain of albino rats was observed in a breeding colony; these animals showed jaundice at birth or shortly thereafter which persisted throughout the life of the animal. Bile was absent in the urine. The van den Bergh test suggested a hemolytic type of icterus. Red cell count was 3.9 million compared with controls of 4.4 million. The urobilin excreted in the feces was sometimes greater than in the normal animals. Marked nervous symptoms developed in some of the jaundiced rats, similar in character to those found in normal rats reared on a vitamin A deficient diet. No gross lesions of the cord or the peripheral nerves was noted. The jaundiced condition is inherited as a non-sex-linked recessive character. Although enlarged spleens were found in 20 per cent of the young, splenectomy did not alleviate the jaundiced condition.—J. M. Theone.

HARD, H. L., AND CARR, C. J.: *Experimental diabetes produced by alloxan.* (*Proc. Soc. Exp. Biol. Med.*, V. 55, P. 214, March, 1944.)

Twenty-four hours after injection of a suitable amount of alloxan into rabbits, rats, and dogs, the blood sugar reached a diabetic level which persisted for weeks. Liver glycogen determinations were normal, suggesting that carbohydrate storage (as glycogen) in the liver is unchanged. It is suggested that the blood sugar rise may be due to adrenal stimulation. Gross appearance of the pancreas, liver, adrenals, and kidneys was normal. Histological changes noted were a pyknosis of beta cells with alpha cells unaffected and a shrinkage of the cells accompanied by degranulation. There were no histological changes in the liver or kidneys. Noticeable changes were seen in the marked fragmentation and shrinkage of the cells in non-localized areas of the medulla of the adrenal gland. However, in permanently diabetic animals the adrenal medulla is normal with the exception of cytoplasmic vacuolation of cells in small areas. The number of islet cells was normal, but many were small and consisted entirely of alpha cells. With the amelioration of the diabetes, however, regeneration of functional cells is possible. The changes in the adrenal medulla and the cells of the islets may explain the character of the acute stages.—R. L. Burdick.

MULLIGAN, R. M., LONGWELL, B. B., AND MORRELL, R. M.: *Tissue changes produced by estrone injected into female dogs with bile fistula.* (*Am. J. Path.*, V. 19, P. 861, 1943.)

Three dogs provided with bile fistulas were given estrone. The iron-containing pigment was found to be increased in the Kupffer cells of the liver, and in the spleen and bone marrow. The bile canaliculi of the liver contained relatively more iron-free pigment. Estrogenic stimulation of the vagina, endometrium and endocervix was also noted.—G. Klenner.

KLURFELD, GEORGE: *Changes in blood chemistry in the rabbit as indicative of hepatic damage by ortho-amidoazotoluol.* (*Helvetica Med. Acta*, V, 11, P. 709, 1943.)

Treatment of rabbits with 5 per cent oily solution of ortho-amidoazotoluol per os or subcutaneously inhibits the weight gain through a reversible inhibition of assimilation. The erythrolytic function of the liver and the synthesis of cholesterol from oleic acid are decreased. Bilirubin values of the serum are not changed, while the bile acid concentration increases. After subcutaneous injections, there is a transient increase in blood sugar. No changes could be detected histologically in the liver.—Courtesy Biological Abstracts.

METABOLISM AND NUTRITION

DORMER, B. A., AND M. GIBSON: *Vitamin A deficiency in tuberculosis and diabetes, and the effect of various therapeutic preparations.* (*S. African Jour. Med. Sci.*, V, 7, P. 109, 1942.)

Using the Frober Fayor biophotometer, investigations were carried out on 3 groups of human subjects to determine the relative incidence of vitamin A deficiency. Only a small per cent of 92 apparently normal young adults were sub-normal; a much larger per cent of 86 tuberculous individuals were sub-normal, the deficiency being roughly proportional to the severity of the pulmonary infection; all of 10 diabetics were sub-normal and could not be adequately corrected by therapy.—Courtesy Biological Abstracts.

BOUWELL, R. K., GEYER, R. P., ELEHJEM, C. A., AND HART, E. B.: *Effect of flavor on nutritive value of fats.* (*Proc. Soc. Exp. Biol. Med.*, V, 55, P. 153, March, 1944.)

Groups of rats were kept on diets of butter-fat and corn-oil, both with and without the flavoring element, diacetyl, and with lactose as the sole carbohydrate. Growth and food intake were greater with the rats fed on butter fat; but the presence or absence of diacetyl had no effect on the nutritive value of the food. Rats kept on butter-fat or corn-oil with and without diacetyl but with dextrose as the sole carbohydrate, showed an increase in growth and food intake over those rats fed on the lactose-fat diets. Here, again, the presence or absence of diacetyl had no nutritive effect. It was concluded that the flavor of a diet does not determine significantly the nutritive value of the diet.—R. L. Burdick.

SPECTOR, S., MCKHANN, C. F., AND MESERVE, E. R.: *Effect of disease on utilization of vitamin A.* (*Am. J. Dis. Child.*, V, 66, P. 376, Oct., 1943.)

A number of factors assisting or governing the absorption of vitamin A are given. The absence of bile salts reduces greatly its absorption from the intestine. It is believed that a fatty acid-vitamin A complex is formed and absorbed through the intestinal wall. Interference with fatty acid absorption, or with the production of fatty acids by digestion of fat, thus interferes with vitamin A absorption. Low vitamin A ab-

sorption is thus explained in conditions where pancreatic enzymes are excluded from the small intestine. Non-absorbable oils, such as mineral oils, hold the vitamin A in solution and do not permit its absorption. Infection seems to alter the capacity of the intestine to absorb the vitamin; and in some chronic infections, such as post-nasal infection, the vitamin A deficiency may become very marked.—I. M. Theone.

MISCELLANEOUS

HACKETT, W. R.: *The pepsin content of gastric juice.* (*J. Pathol. Bacteriol.*, V, 56, P. 136, Jan., 1944.)

The peptic activity of a sample of gastric juice is expressed in terms of concentration of pepsin by referring the digestion activity, using serum albumin as a substrate, to a previously prepared chart. Given sufficient time, the weaker concentrations of pepsin hydrolyze serum albumin as well as the stronger concentrations do. No activity occurs in an alkaline medium, but activity is little retarded even with a pH as high as 6.0.—D. A. Wocker.

DIMTER, A.: *Unsaponifiable matter in the fetal and adult liver.* (*Hoppe-Seyler's Zeitschr. Physiol. Chem.*, V, 271, P. 293, 1941.)

Analysis of the unsaponifiable matter from fetal and mature mammalian livers showed that in the former, cholesterol is predominant while in the latter paraffin hydrocarbons of the squalene type were found. Vitamin A and lipochrome were abundant in mature livers. The hydrocarbon, called "hepene," after reaction with HCl or HBr has the formula $C_{30}H_{48}$, $SHCl$ or $C_{30}H_{46}$, $12HBr$, showing it to be of squalene type. The hydrocarbon was absent in body fats, blood and bile. The author concludes that "hepene" is an intermediate in the formation of cholesterol in extrauterine life.—Biological Abstracts.

MACLAY, E. AND OSTERBERG, A. E.: *An adaptation to the colorimeter of the Sepulveda-Osterberg serum bilirubin procedure.* (*Proceed. Staff Meet. Mayo Clinic*, V, 19, P. 4, Jan. 12, 1944.)

The procedure described omits the necessity of a photo-electric colorimeter if one is not available. A solution of 600 milligrams cobaltous sulfate is equivalent in color intensity to a solution of 1 milligram bilirubin in 100 cc. Matching the serum bilirubin against the cobaltous sulfate has given readings of 0.3 to 2.0 milligrams bilirubin per 100 cc. Higher concentrations of bilirubin are diluted to fall within this range.—I. M. Theone.

STEIGMANN, F., AND MARKS, A. R.: *Clinical studies on a new pepsin inhibitor.* (*Proc. Soc. Exp. Biol. Med.*, V, 54, P. 25, Oct., 1943.)

Peptic ulcer patients were given an Ewald test meal plus calcium carbonate, aluminum hydroxide or sodium lauryl sulfate. Regardless of the initial pH and peptic activity of the gastric contents the calcium carbonate and aluminum hydroxide caused the greatest rise of pH and the greatest decrease in peptic activity. One

hundred mgs. of sodium lauryl sulfate had no significant effect on either the pH or the peptic activity; administration of 200 mgs. of sodium lauryl sulfate or its administration on successive days caused a slight rise in pH and a slight lowering of peptic activity. In all cases, 2 hours after the administration of the pepsin inhibitors, the pH and peptic activity values returned to those obtained with the test meal alone. It was concluded that sodium lauryl sulfate does not act *in vivo* as an inhibitor of pepsin unless the pH of the gastric contents is raised.—R. L. Burdick.

FORBES, J. C., AND EVANS, E. J.: *Protective action of sulfanilamide from chloroform liver damage.* (*War Med.*, V. 4, P. 418, October, 1943.)

A distinct limitation to the use of chloroform as an anesthetic is its damaging effect on the liver in certain cases. In naval medical practice the use of chloroform would be desirable because of its low bulk, non-inflammability, and relative simplicity of administration. The authors found in animal experiments that some degree of protection against liver damage by chloroform inhalation is exerted by previous oral administration of sulfanilamide. Inasmuch as the sulfa drugs, particularly sulfanilamide, are used widely in the war-wounded, the subject for operation will already have had some protective treatment before chloroform anesthesia. It is, however, desirable that the sulfanilamide treatment be instituted early enough to assure a high concentration of the drug in the blood and liver at the time of anesthesia.—G. Klemmer.

BERRIDGE, N. J.: *Pure crystalline rennin.* (*Nature*, V. 151, P. 473, 1943.)

The crystallization of an enzyme is not proof that the enzyme is pure, it is only supportive evidence that purification has proceeded to a high degree. A preparation of rennin was made consisting of flat crystals and also spheroids. The solubility was independent of its rennin activity or its total nitrogen content. Probably no major impurity was present. The crystalline rennin was prepared by precipitating rennet at pH 5.4 with saturated NaCl and adsorbed on alumina formed by addition of potash alum. Salting out and re-dissolving were repeated several times. Final crystallization was achieved by the slow addition of saturated magnesium sulfate.—F. E. St. George.

KIRSNER, J. B. AND WOLFF, R. A.: *Effect of sodium alkyl sulfate on peptic activity of gastric contents in man and in vitro.* (*Proc. Soc. Exp. Biol. and Med.*, V. 54, P. 11, Oct., 1943.)

Experiments done *in vitro* with gastric juice and sodium alkyl sulfate showed that the detergent eliminated peptic activity with very little deviation of pH. When 20 per cent cream was added *in vitro* to gastric juice and sodium alkyl sulfate, the inhibitory effect of the detergent was greatly decreased. The decreased inhibitory effect was also found when lecithin was added

while the effects of lard and mineral oil were not noticeable.

Experiments performed *in vivo* on 3 male patients with duodenal ulcers gave the same results. When the patients were given a diet low in lipids, sodium alkyl sulfate inhibited peptic activity. When the patients were given cream, the inhibitory effect of the detergent was eliminated.

It was found that the pepsin-inactivating action of sodium alkyl sulfate is inhibited *in vitro* by cream, butter, lecithin, glycerin, and esters of fatty acids, while lard, mineral oil and olive oil are practically ineffective in this respect.—R. L. Burdick.

VOLK, B. W. AND POPPER, H.: *Microscopic demonstration of fat in urine and stool by means of fluorescence microscopy.* (*Am. J. Clin. Path.*, V. 14, P. 234, April, 1944.)

The alcohol in Sudan III stain dissolves some of the fat, therefore a water soluble fluorescent fat stain, "Phosphin 3R," was used. A loopful of feces or centrifuged urine sediment was suspended in one drop of the Phosphin 3R stain, and examined under a fluorescence microscope. The details of this microscope are given, but essentially it is constructed to eliminate all but the ultraviolet light rays. The fat droplets were easily seen and identified, giving much better results than Sudan III.—Wm. O. Beamer.

HESS, M. AND HOLLANDER, F.: *Permanent metachromatic staining of gastric mucus smears.* (*J. Lab. Clin. Med.*, V. 29, P. 321, March, 1944.)

The purpose of the investigation was to find a method for staining smears of gastric mucus so that the cellular structures would be visible by contrast against the background of mucous material.

The important factor in the method devised was the use of a fixative ($HgCl_2$) after the slide has been stained, since its use before staining was ineffective. Mild acidification of the dye solution with hydrochloric acid increased the color contrast between nuclear material and the mucus; this was not true, however, when other acids were used. Sulfuric acid was also added to the dye solution to increase the intensity and substantiability of the staining. Use of hydrochloric acid alone resulted in loss of dye during the later steps; sulfuric acid and hydrochloric acids used together, however, prevented this loss.

In finished preparations both extra- and intracellular mucus stain purplish-red while the cells stain blue with the nuclei having the greater depth of blue.—R. L. Burdick.

HANSEN, L.: *Defects of ocular muscles in chronic colitis.* (*Deutsch. med. Wochenschr.*, V. 67, P. 1017, 1941.)

Weakness of convergence and presence of hemeralopia in a patient with chronic colitis is tentatively explained as a result of symptomatic sprue and degeneration of supranuclear tracts.

Relationship Between the Lymphoblastic Tumor and the Digestive Tract*

By

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THE term "lymphoblastic tumor" includes two main varieties: the lymphogranuloma, first described by Hodgkin, and the lymphosarcoma, first described by Kandrak. Although the two tumors vary distinctly in their histological structures, they have a number of features in common, making them indistinguishable clinically. Both develop in the lymphatic tissue and may spread throughout the entire lymphatic system. However, different parts of the lymphatic system are, in varying frequency, sites of either of the two varieties. On one hand there are regions which almost invariably are affected. Here, for instance, belong the neck or the mediastinum. On the other hand there are regions in which lymphoblastic tumors are found much less frequently. Here belong the lymphnodes surrounding the digestive tract from the pharynx down to the rectum. As a consequence, the symptoms on the part of the digestive tract caused by these tumors are not so well known, and in many textbooks not even mentioned.

In the last few years I have had the opportunity of seeing eight cases with lymphoblastic tumors affecting the digestive tract, and should like to report on the findings in these cases.

The *clinical* symptoms are functional disorders of the digestion in dependence on the *localization* of the tumor.

When the tumor is in the vicinity of the pharynx or esophagus, difficulty in swallowing results.

When the tumor is in the vicinity of the stomach or duodenum, vomiting follows.

When the tumor is in the vicinity of the rectum, constipation develops.

The *radiological* signs concern the morphological appearance of the digestive organs in dependence on the *size* of the tumor.

When the tumor is small, an indentation of the contours results.

When the tumor is of larger size, there is also a displacement of the affected organ.

When the tumor is very large, an occlusion of the lumen is produced and symptoms of stenosis develop.

As to the treatment, Roentgen therapy has proved the method of choice. The effect sets in in the course of a few days, and a complete disappearance of the tumors may be obtained in the course of a few weeks. Radiotherapy removes the immediate danger to life, and is therefore a life saving measure. Needless to say that, nevertheless, the final outcome of the disease still leaves much to be desired.

The observations made in five cases representing lymphoblastic tumors affecting different parts of the digestive tract may be quoted for illustration.

The first case concerns a patient with Hodgkin's disease. The twenty-four year old man came because of increasing difficulty in swallowing. When he opened his mouth a protrusion of the posterior wall of the oro pharynx was noticed. An X-ray film of this region shows that the transparent band representing the air-containing parts of the pharynx was considerably displaced to the left. (Fig. 1) The diagnosis as to the

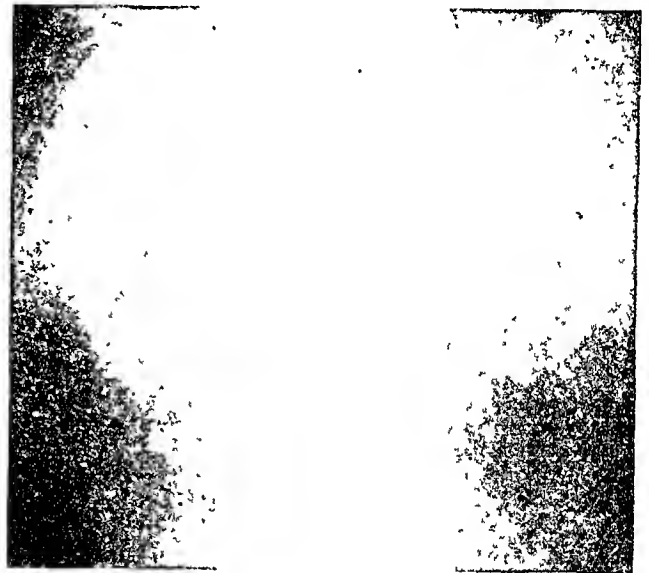


FIG. 1

The oropharynx is displaced to the right by a mass on its left side.

nature of the tumor was made by means of a biopsy of an indolent, hard lymphnode found on the same side of the neck on which the pharyngeal tumor was present. X-ray therapy caused the disappearance of both, the pharyngeal and the cervical tumor. (Fig. 2) Curiously enough, the wall of the pharynx opposite to the tumor did not return to its normal position presumably because adhesions developed during the period of dislocation. The patient remained locally symptom free during a two-year-long observation, but developed lymphnodes on the other side of the neck and in the mediastinum which were treated with rays.

The second case likewise concerns a patient with Hodgkin's disease. The twenty-eight year old woman suffered from lymphnodes in numerous regions of the body, which disappeared following X-ray therapy. Some time later she started complaining of difficulty in swallowing. A mediastinal tumor was thought of but was not found on X-ray examination. However,

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when the esophagus was filled with barium, an indentation on the right side was disclosed, typical of

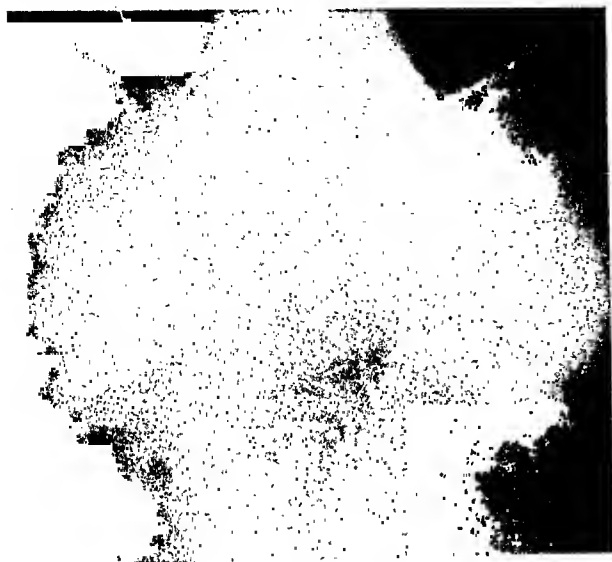


FIG. 2
Same case as Fig. 1 after X-ray therapy.

pressure produced by an extrinsic tumor. (Fig. 3). X-ray therapy caused a disappearance of the tumor so



FIG. 3
The esophagus shows an indentation of its left side due to an extrinsic mass.

that the esophagus regained its normal shape and position. (Fig. 4).

The third case concerns a patient with a lymphosarcoma. The fifty-seven year old man was treated with X-rays over one and a half years in the mediastinum,

axillary, and inguinal nodes when he began to complain of fullness in the stomach and vomiting. X-ray examination showed that the stomach was pushed to the left and that there was an angulation between the



FIG. 4
Same case as Fig. 3 after X-ray therapy.

cardiac and middle portion of the stomach (Film 5). X-ray therapy in this case also caused a disappearance of the tumor so that the patient ceased to vomit and the stomach regained its normal appearance. (Fig. 6).

The fourth case likewise concerns a patient with lymphosarcoma. The fifty-four year old man first had a mediastinal tumor with pleural effusion which was successfully treated with X-rays. Six months later he returned in a very bad condition. He had severe pains in the back and vomited almost everything he ate. X-ray examination revealed a complete stop of the barium flow at the transition of the second to the third portion of the duodenum with a marked prestenotic dilatation (Fig. 7). X-ray therapy had a prompt effect on the symptoms, subjectively as to the pain, and objectively as to the return of the normal passage through the duodenum (Fig. 8). The mediastinal tumor recurred, however, and caused the death of the patient shortly afterwards.

The fifth patient, a thirty-two year old woman, complained of severe pain in the lower back. Gynecological examination and X-ray films of the pelvis and lumbar spine were negative. Careful questioning elicited that there was also constipation in the last few months. Barium enema disclosed that the rectum showed an indentation and angulation on its right side, which at first could not be explained satisfactorily (Fig. 9). However, on careful examination a few lymph nodes were found in both inguinal regions. One of the nodes



FIG. 5
The stomach shows a sharp angulation between its cardiac and medial part.

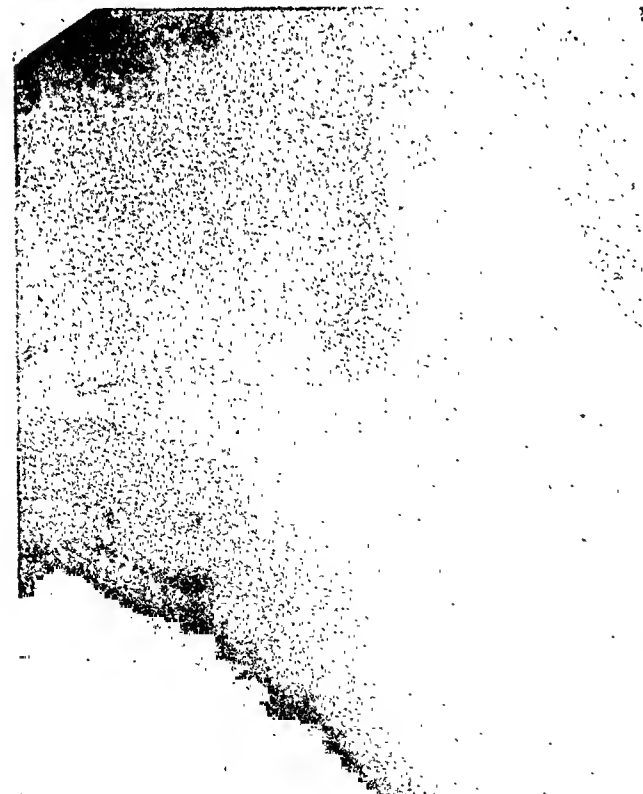


FIG. 7
The duodenum shows a stop between the second and third part (lateral view).



FIG. 6
Same case as Fig. 4 after X-ray therapy.

was excised and proved to harbor a tissue described as "probably a lymphosarcoma". X-ray therapy was instituted and made the tumors disappear, those in the inguinal regions as well as that compressing the rectum. As a consequence, the constipa-



FIG. 8
Same case as Fig. 7 after X-ray therapy.

In conclusion, we see that lymphoblastic tumors may produce definite symptoms on the part of the digestive

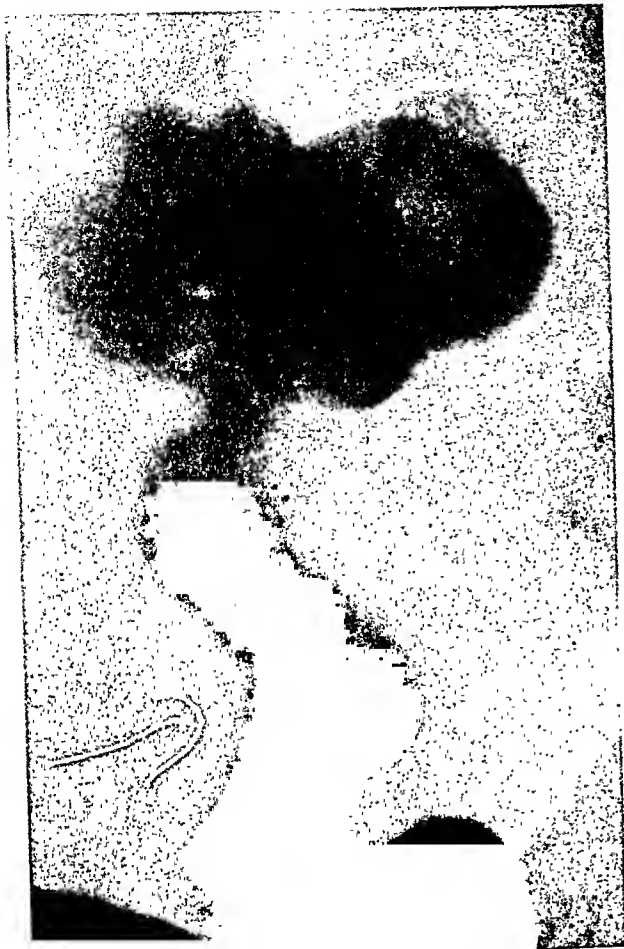


FIG. 9

Showing a sharp angulation of the right contour of the rectum. tion disappeared and the rectum regained its normal appearance (Fig. 10).



FIG. 10

Same case as Fig. 9 after X-ray therapy.

part which can be definitely diagnosed and then successfully treated with X-rays.

On the Absorption of Iron*

By

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and

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AS WILL be seen in the course of this review, the absorption of iron is a gastro-intestinal phenomenon in which the acidity of the gastric and duodenal contents undoubtedly plays a part. Consequently in cases of widespread gastric resection the conditions for successful iron resorption have been definitely altered. The mystery of the absorption of iron in these cases, and indeed in normal ones, has not been entirely solved, but the view set forth below is an undoubted guide to the administration of iron for therapeutic purposes. Unfortunately absorption is but the prelude to the use

of the iron absorbed, which depends on other factors, copper doubtless in part, vitamins and the state of the bone marrow.

The reputation of iron as a medicament was perhaps chiefly based on its curative action in chlorosis. This old-fashioned disease seems to have disappeared with the abandonment of tight lacing. But there are still many cases of hypochromic anaemia, due either to deficiency in iron absorption or undue loss, together with a considerable percentage of cases of inadequate utilization.

The literature on the subject since the time of Bunge has increased enormously and no review can adequately

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Submitted January 28, 1944.

ly deal with all phases of the subject. Only those papers will be dealt with which seem to be of definite determinative value.

The most fundamental contribution to our knowledge of the form in which iron is absorbed from food is that of Lintzel (1). It was known that alpha-alpha-dipyridyl forms a complex with ferrous, but not with ferric iron. Lintzel showed that the dipyridyl was not toxic to rats when injected and appeared rapidly in the urine to the extent of some 12%. If the ferrous iron complex were injected, it, too, appeared rapidly in the urine to the extent of some 38.50%, but none in the faeces. Now if he fed rats on a diet containing ample available iron as judged by the increase in iron in the body and growth of the normal controls, while other rats were fed alpha-alpha dipyridyl in a quantity adequate to unite with all the iron were it converted into the ferrous form, the rats failed to increase their bodily content of iron and growth also failed. Further, none of the ferrous dipyridyl complex appeared in the urine. Lintzel concluded that absorption of iron only occurred in the ferrous form since the dipyridyl would not prevent the absorption of ferric iron. This experiment was repeated by Lucas and Summerfeldt (2), who showed that the animals fed the dipyridyl became rapidly anaemic, the haemoglobin falling from an average of 11.6 to 6.03 Gm.

It is, however, well known that the administration of ferric iron, for example as the perchloride, will raise the haemoglobin in anaemia. And indeed, as Lucas and Summerfeldt showed, if rats were made anaemic by deficient iron feeding, adequate amounts, 0.25 mgm. iron per diem as either ferric or ferrous chloride, led to an equal gain in haemoglobin, as did Iron and Ammonium Citrate, but if the amount of iron were reduced to 0.05 mgm. iron the gain produced by Iron and Ammonium Citrate was roughly only 1/3 of that produced by either ferric or ferrous chloride and when 0.025 mgm. iron was fed the gain with ferrous chloride was ample, while that with ferric was slight. It therefore becomes pertinent to examine what is known about the fate of medicinal iron in the stomach.

1. *Ferrous Sulphate or Ferrous Chloride.* (Available in a stable form as the Citrated Ferrous Chloride B.P., which is not a complex salt, but in solution liberates free ferrous iron). These are not precipitated by proteins, nor at a pH of lower than 5 by carbonates; even about this pH more ferrous than ferric remains in solution (Halvorsen and Starkey (3)). This is important, as the gastric contents poured into the duodenum, change rapidly from a low pH to one of 7 and upward, (McClure et al (4)), and consequently very rapidly ferrous, and even more rapidly ferric, ions will disappear, insoluble forms being produced. In the lower part of the gut, with still higher pH and the presence of much carbonate and sulphides, precipitation will occur and no available ferrous ions will be found. It should, however, be remembered that Starkenstein (5a) has shown that ferrous salts can be absorbed from the stomach in rabbits.

Bland's Pill contains the insoluble ferrous carbonate. This can be readily converted into ferrous chloride by

hydrochloric acid and made soluble less readily by carbonic acid and by fatty acids. There is little doubt that the precipitated form is not available, but only such as is transformed into a soluble ferrous form.

Reduced Iron. This is so called because it was reduced from the oxide. In the presence of hydrochloric acid, ferrous chloride is produced, but no ferric as long as any iron remains undissolved. Bauer (6) has shown that as the concentration of hydrochloric acid increases, the amount of iron dissolved increases, but not proportionately, and if the concentration of acid is constant, the amount of iron dissolved increases as the amount of iron increases, but again not proportionately. Reduced iron is slowly attacked and becomes dissolved by carbonic acid and by organic acids, but the amount dissolved by organic acids varies with the acid and is greater in some cases than would be expected from the pH. Hence a probably small proportion of Reduced Iron administered will become ferrous iron and the proportion will probably be less in the achlorhydric patient.

2. *Ferric Iron.* Ferric Chloride readily precipitates proteins. The protein iron complex probably only frees iron ions after protein digestion has proceeded, when the presence of carbonates will lead to precipitation. This reaction with proteins is probably the cause of ferric chloride producing gastric irritation and hence is little employed today. Further, as we have seen, a pH of even 5 leads to extremely few ferric ions remaining in solution. So far the evidence would suggest that ferric chloride would be an extremely poor source of iron. It was, however, shown by Starkenstein (5b), Sullmann (7) and others that in the food in the stomach, reducing substances such as glutathione, and some of the amino acids, are available, which reduce ferric to ferrous ions; ascorbic acid will do the same, and this was confirmed in the case of ferric iron by Moore, Arrowsmith, Welch and Minnich (8), who showed that iron absorption was greater if ascorbic acid were fed or if the reducing agent, formaldehyde sulphoxate, were added to diet.

3. *Complex Iron Preparations.* Of these we need only consider Iron and Ammonium Citrate. This in solution shows no iron ions, but in the presence of hydrochloric acid, even in very low concentrations, liberates ferric ions. The fate of the ferric ions liberated will then resemble those of ferric chloride. Some will be reduced to ferrous and become available, the greater part will not. We have not, however, any adequate explanation of why this salt can raise the haemoglobin in a case of achlorhydria. Free iron ions are not liberated from this salt by carbonic acid. We know that lactic acid will do so, but this is one of the stronger organic acids (personal experiments). Nor does it seem likely that any of the amino acids would produce this change, as acetic acid does not. We have, however, found that ascorbic acid leads to the appearance of ferrous ions, though we are not sure that this will occur when the ascorbic acid is present in the food. The complex has, however, another characteristic which differentiates it from the inorganic preparations, namely, it is not precipitated by carbonates or phosphates and consequently

is available for absorption over a greater length of the gut and were it to be absorbed as a complex it might act as a source of iron, since it is known that when injected as the green salt it will lead to haemoglobin production according to Heath, Straus and Castle (9), who used very large doses, 16-32 mgm. of iron (or 213 mgm. of the salt) of which 96% was utilized in haemoglobin production. Their two cases varied from 66-154%! Fowler and Barer (19), treated cases of hypochromic anaemia with intramuscular doses of 0.1 Gm. (1.5 mgm. of iron) for 12-24 days and showed that while they retained all the iron injected, there was no increase in haemoglobin in three out of four cases and slight in the other, though the erythrocyte count increased slightly and there was a small, 1-3.2%, output of reticulocytes. Two of the patients showed a rapid gain when 3 Gm. Iron and Ammonium Citrate was given per os. There is, however, little doubt that the amount of iron usually given by injection is almost completely valueless as compared with the amount that can readily be absorbed per os.

If the above description of the changes in the ordinary forms of medicinal iron is correct, as it seems to be, then we have probably accounted for the production of adsorbable iron in all cases save that of Iron and Ammonium Citrate in a case of achlorhydria.

Further, if this picture is correct, the importance of hydrochloric acid is evident and on this point there is certain experimental evidence. Mettler and Minot (11) fed ground up beefsteak digested in vitro at 37° for two hours with hydrochloric acid and pepsin. To the strained material Iron and Ammonium Citrate, 0.5 Gm., was added either before or after neutralization to pH 7-8. This was given to ten anaemic patients by stomach tube for from 9 to 15 days. The neutral form produced less effect on reticulocytes, haemoglobin and erythrocytes than the acid form. Heilmeyer and Plotner (12) failed to get any effect in certain achlorhydric patients from Reduced Iron when Ferrous Sulphate gave a good response. Moore, Doan and Arrowsmith (13) showed that in an achlorhydric case the serum iron increased less with a large dose, 5 Gm. of Reduced Iron, than when hydrochloric acid was given with the same amount of Iron. Kellogg and Mettler (14) found in ulcer cases on a Sippy alkalization diet, no or but slight increase in reticulocytes or haemoglobin when food containing adequate iron was given, while without the alkalis definite responses were obtained. Minot and Heath (15) state that there is a definite tendency for achlorhydrics to show a smaller reticulocyte response to Ferrous Carbonate or Iron and Ammonium Citrate in equal doses of iron, and a smaller gain in haemoglobin and erythrocytes than in chlorhydrics, and this agrees with the slower gain in such cases observed by Witts (1931).

The dosage required. Even in the case of hypochromic anaemia the dosage of any preparation cannot be definitely laid down. The reason for this will be considered later. A consideration of the literature leads one, however, to agree with Witts (16), Moore, Arrowsmith et al (8), and with Widdowson and McCance (17) that ferrous iron gives a better response

than the same amount of ferric, and this is evident in the work of Reimann and Fritsch (18). Accurate quantitative comparisons carried out on either the same individual or on a series of cases with all the usual iron preparations are not available. But good responses in haemoglobin and erythrocytes occur with daily doses of:—

Drug	Gm.	gr.	mgm. Iron
Ferrous Chloride	0.35-0.7	5-11	100-200
Sulphate	0.5-1.0	7-15	100-200
Blaud's P II	3-4	45-60	300-400
Reduced Iron	1.5-6	22-90	*1200-1500
Iron and Ammonium Citrate	4-8	60-120	**800-1600
Solution of Ferric Chloride	4-8 mls	60-120 min.	200-400

This Table agrees approximately with Witts (19).

* Based on B.P. iron values. U.S.P. doses of Reduced Iron would be smaller, 1.3-5.2.

** U.S.P. dose would have to be larger by 1/5 to give the same iron value.

But this is by no means the complete story, as we shall produce evidence to show that there is an absorption and storage of iron with all forms of medication which is greatly out of proportion to the amount of haemoglobin produced and in some cases without bringing the haemoglobin to a normal value with such doses, even when larger doses will do so.

The daily required intake of iron is low. Lintzel (20) and Widdowson and McCance (21) produce evidence that not more than 1 mgm. is necessary in males. Ordinarily this is obtained from food. While there is evidence that anaemia in males does not usually occur with a supply of 5-7 mgm. of food iron, this is certainly too low a figure for many women who are menstruating, quite apart from pregnancy. The menstrual loss of iron has been found to show a wide variability. Widdowson and McCance (21), 3.6 mgm., 28.0, 11.0 per period in three cases who showed fairly constant amounts at each menses; Ohlson and Daum (22), 18.16, 25.68, 32.35, 41.9, for example. If only 1 mgm. were being absorbed daily, the menstrual loss might exceed the total intake, and there is certainly a small loss in the urine, measurable at least when the intake is high. According to McCance, it is doubtful if there is any excretion by the gut, as has so long been taught. All the evidence suggests that this is correct.

The iron in the food differs much in its availability for absorption. We know, for example, that haemoglobin is a very poor source of iron, while spinach and green cabbage are good sources (Lintzel (20)). And until more exact studies are made on food after cooking, and indeed after digestion, it seems that at least 10 mgms. are required and most nutritionists put the figure at 15 mgms. daily. Even in normal women this should cover menstrual losses, but hardly seems adequate from clinical observation to cover the more rapid loss to the foetus in the late stages of pregnancy. Consequently it must be admitted that a daily intake of 15

mgms. in the food should be provided, though for most persons 10 mgms. would be ample.

Enough studies with careful measurements of the amount of iron in the form of food and medicine, of the amount of iron absorbed and the amount utilized in the formation of haemoglobin, have been made to make it clear that the whole mystery of the utilization of iron in the building of haemoglobin has not been solved. Such studies are to be found in Fowler and Barer (23), Brock (24), Widdowson and McCance (17), Marsh, Leverton et al (25), Brock and Hunter (26). But these studies, as well as others which will be referred to, make it evident that certain principles of iron medication must be understood by the physician and must serve to greatly modify his treatment in many cases. They also serve to indicate that such a Table of Dosage, as has been given above, must often be departed from.

One example (Fowler et al) will serve to illustrate all these observations. A female patient, idiopathic hypochromic anaemia, 4.45 million erythrocytes, haemoglobin 6.15 Gm. (i.e. about 46%), when on a diet with 11.9 mgm. of iron and a daily loss of 0.1 mgm. was given 1 Gm. (15 gr.) of Iron and Ammonium Citrate 3 times a day for 24 days. The total of iron consumed, food and medicine, was 12.411 Gm. of iron; of this 8.854 Gm. was retained. In other words, she retained 71.3% of the iron fed, but utilized for the formation of haemoglobin only 1.09% of the iron given or 1.53% of the iron retained. Her haemoglobin increased to 7.95 Gm. %, (about 70%). It might be thought that not enough time had been given for the iron to be transmitted into haemoglobin, but this is certainly not the explanation as some of the iron was converted rapidly into haemoglobin.

An examination of many recorded cases of hypochromic anaemia reveals that though fairly adequate gains in haemoglobin, up to 70%-80% of haemoglobin, and erythrocytes takes place with moderate doses, such as suggested, no further progress is made unless the dose is greatly increased. On the first administration of iron (Minot and Heath (15)), there is a definite increase in reticulocytes, but these decrease again even if haemoglobin and erythrocytes increase slowly. Again, when the dosage is increased, there is a fresh production of erythrocytes and further gain. Yet it has been shown in many cases that iron is being stored by the patient throughout the whole course of treatment so that there are ample iron stores for a great production

of haemoglobin. In some cases the failure in haemoglobin formation may be as shown by Heath (27), due to an infection, but this does not apply in many cases (Brock; Wits; Brock and Hunter; Heilmeyer and Plotner). Nor, as Heath and others have shown, is it due to a lack of copper or of the haematopoietic principle of the liver. Fuhr and Steenbock (28) presented evidence that vitamin D may increase the utilization of iron in rats under certain experimental conditions, and there are certain cases where vitamin C is effective (possibly for the reason suggested above), but this is not true of many of the cases. It is evident that an increased intake of iron has a direct, but temporary, stimulating effect on the bone marrow as pointed out by Minot and Heath (15), and observed by many others, but this may not be accompanied by a proportionate formation of haemoglobin. We know very little of what happens to iron after absorption, but it was shown by Starkenstein and Harvalk (29) that ferrons iron added to blood in vitro, under the influence of globin and haemoglobin, is transformed rapidly into a ferric complex form so that iron ions rapidly disappear. This compound may cause the initial bone marrow stimulation, even if this iron form has to undergo further elaboration before it is available for haemoglobin formation. Further than this, speculation seems unjustified.

But for the ordinary clinician it seems obvious that the most generally useful forms of iron for administration are either Ferrous Chloride, preferably when given in a mixture with syrup and hypophosphorous acid, which delay oxidation, or the Citrated Ferrous Chloride may be used in the same way, or Ferrous Sulphate, particularly in achlorhydric cases. We have known cases showing an excellent response from pills containing 300 mgm. (5 gr.) of the Citrated Ferrous Chloride daily. In a case with hydrochloric acid, any iron preparation will be successful if the dosage is adequate for the particular case. Adequate dosage can only be measured by the response. In infants with low iron intake, the addition of copper may be of benefit, but for adults this does not seem to be required. Further, most iron preparations contain enough copper as impurity to meet all needs.

It should be noted that the first symptom due to an excess of ferrons iron is diarrhoea; further that ferrous mixtures may lead in some persons to a black deposit on the teeth, which is readily removed with the tooth brush.

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The Neurotic Patient. A Discussion of the Causes and Treatment of Neurosis*

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WITHIN the past decade the neurotic patient has come into his own. No longer is he considered to be a sort of malingeringer who makes excessive demands upon the time and patience of the physician with his seemingly endless recital of symptoms; rather he is now regarded as being a sufferer of psychosomatic disease which calls for fine diagnostic inquiry into the etiology of his ailment and an equally painstaking plan for treatment.

When a patient says that something hurts him, the physician unfortunately can neither prove nor disprove the statement. Pain being a psychic phenomenon is not measurable by any instrument of precision. There is simply no way of recording the intensity or even the existence of pain, save only in the consciousness of the individual. Hence when a patient states that he has pain, there is no point to challenging him or belittling him or telling him that it is imaginary, since the whole process of pain takes place within the domain of the individual's mind.

The incidence of psychoneurosis is determined by the ability of the physician to recognize it. Unlike hernia, typhoid fever or other organic diseases, it does not always carry a distinctive label. Some physicians maintain that they see very little of psychoneurosis; however others have stated that thirty percent of all patients who come to the physician's office have some psychoneurotic angle to their problem.

One of the annoying aspects of the neurotic patient is that he is often more interested in his symptoms than in their treatment; indeed he seems to revel in the repeated recital of them. He is anxious that the physician shall grasp the full importance of the last detail of his ailment. When this occurs the diagnosis of a neurosis is almost self evident. However not all cases are as clear cut as this, also there is a large group of patients who present both organic as well as neurotic symptoms, in whom the signs and symptoms are so overlapped and interwoven that it often requires fine diagnostic judgment to separate them.

But what is a neurotic? A neurotic is obviously a person suffering from a neurosis. And what is a neurosis?

A neurosis is a psychic phenomenon in which an individual has become maladjusted to some life situation and reflects the conflict in his state of health. Somewhere in his pursuit of a livelihood, or in the struggle for existence or power, the individual has encountered one or more obstacles which have interfered with the achievement of his desired goal. The stress and strain of living, the velocity and complexity of a changing civilization have proved too much for him so that he has suffered defeat or become embarrassed, confused, frustrated or maladjusted. The external conflicts become expressed within him, first as psychic manifestations as tension, apprehension, uneasiness, introspection, fear, worry; then as focal or general symptoms as coated tongue, epigastric distress, palpitation, etc. The neurotic is a person who is out of step with some life situation and reflects it in his state of health.

There is a wide difference of opinion as to who are neurotics and what constitutes a neurosis. On one extreme are the adherents of the organic theory of disease who maintain that most diseases have an organic basis. These organicists assert that if you but look hard enough and long enough some organic abnormality will be found to explain the symptoms. However Alvarez cautions that these incidental occurrences as ptosis, low blood pressure, low blood sugar, etc., merely provide a diagnostic placebo while the real cause must be sought in the central nervous system. Weiss believes that about one third of the patients who consult an internist have symptoms that are dependent on emotional factors even though organic findings are present. Sadler states that there are seven thousand babies born every twenty four hours in the United States, and it is disconcerting to know that twelve out of every twenty five who will reach adult life will be more or less neurotic; in other words about one half of all the babies born are destined to be neurotic adults, while Ross states it is becoming more and more evident that minor examples of neuroses are to be found everywhere.

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There is no branch of medicine or dentistry that escapes its quota of neurotics. The manifestations of a neurosis exhibit such an enormous range of mental and physical symptoms that they may be said to reflect the individual's entire reaction to his life's problems.

The symptoms of a neurosis may be general or localized, and any organ of the body may become the focal point of the neurosis. The digestive tract is focused on most commonly, with the circulatory system second; but other organs may also become the focus of attention; thus a facial blemish or a large nose may give rise to an inferiority complex. Large hands or feet may give rise to a behavior problem, a squeaky voice may give rise to a feeling of inadequacy, a dental defect may be the cause of an anxiety neurosis, etc. However neurotics are not necessarily life's failures. Indeed in spite of their neuroses some of them become successful and even leaders in their chosen field.

What are the causes of a neurosis? Two men with similar background suffer the same frustration such as a sudden loss of family income or prestige. One of them develops a neurosis, while the other makes adequate adjustments and seemingly continues to live a normal life. Such a situation directs our attention to the causes of a neurosis.

The causes of a neurosis are manifold, complicated and prolonged in their genesis. It is seldom that a single incident produces a neurosis, although it may appear to do so. Actually it was only the precipitating factor. Adequate inquiry into the behavior problems of the individual will usually show that there was present a sequence of events which prepared the individual for the precipitating factor. The loss of the family prestige was followed by a nervous breakdown, true, but the person had been a candidate for such a breakdown for some time previously.

There are three principle etiologic factors present in the development of any neurosis, namely heredity, environment and training; these comprise the so-called neuropsychopathic triangle. It is a matter of common observation that neurotic tendencies tend to converge in certain families. Heredity, however, transmits only the general characteristic of the behavior tendency, and not its specific expression. Thus a high tension nervous system is a transmitted characteristic, but in one member of a family it may appear as a nervous indigestion while in the next as a cardiac palpitation. Racial characteristics are also transmitted and appear in the individual to influence his personality. Thus the peoples of southern Europe are more temperamental and neurotic than the races of the north. Other examples may be cited.

Among other etiologic factors, the economic life of the individual may be mentioned which makes drastic impressions on him. The complexity of a modern civilization overwhelms certain persons and they find it difficult to maintain the pace required of them in keeping up with the Joneses. Many a person who can carry on successfully in a village may succumb in a city. His nervous system can stand the pace of Main street, but not that of Broadway. Education and sex life likewise make their impressions. The Freudians especially stress

the importance of sex problems with their inhibitions, repressions, etc. Certain organic agents sometimes act as precipitating factors, as toxemias, endocrine imbalances, gastrointestinal disturbances especially constipation; infections as syphilis; likewise degenerative diseases as arteriosclerosis, senility, fatigue, exhaustion, etc. The emotional crises are probably the most common of the precipitating factors, as fear, fright, frustration, worry, anger, hate, confusion, anxiety, etc.; also the guilt feeling, disillusionment, social reverses, economic upheavals, emotional and sex conflicts, nervous strains, domestic infelicity, in fact any of a thousand obstacles which interfere with the achievement of a desired goal.

Not all individuals react to a given situation in the same manner. Even in the case of siblings, the response of the individual to conflict may be entirely different from that of his brother. In the case of siblings one might expect identical inheritance. But Nature never makes two persons in exactly the same mold. At the moment of conception a pattern is created for the individual which is different from all other patterns. No two are exactly alike. This pattern carries with it mental and physical characteristics derived from numerous ancestors of many generations selected for him by Mother Nature according to certain rules of evolution which have served her purpose through the ages. The pattern predetermines for him his sex, his weight and height, his life expectancy, the color of his eyes and hair, his blood pressure, the diseases to which he will be susceptible, his emotional stability, his nervous temperament, as well as numerous other physical and mental characteristics. In short, the neurotic is born predisposed to his neurosis.

Conflict with life situations seems to be the basis of most neurosis. But why must there be struggle in our lives? Because struggle is basic to life itself. Nature knows of no static life. All life is dynamic. All life is a constant succession of changes. All life is a conflict, a struggle for existence with a survival of the fittest. Through struggle, Nature constantly forces out her inexorable laws of evolution. Any attempt to so organize society that it eliminates the element of strife and conflict is purely artificial and unbiologic, and sooner or later must explode from the stress and strain or internal dislocations.

In conflict and in struggle fear occurs and is considered to be an important element which makes for self preservation. Without fear neither the individual nor the race can survive; for survival may depend at times upon quick flight and not upon rash bravado. Fear is a primitive instinct which we of today inherit from our ancestors as a price of their survival. Fear is a normal reaction. Fear is essential to self preservation; but fear can become abnormal when it occupies a place out of proportion to the actual threat to safety. When fear becomes pathological, it gives rise to worry, inadequacy, anxiety states, etc. It becomes a cause of disease and a basis for neurosis.

When a person experiences fear, certain changes take place in his body. Fear transmits its impulse to the sympathetic nervous system which in turn stimulates

the adrenal gland to secrete a small amount of epinephrine into the blood stream which then causes the heart to beat faster, the blood pressure to become increased, the respiration to be quickened, the sweat glands to increase their output, as well as causing other visceral changes in the body.

Irrespective of whether fear has a real foundation or not, it turns in a physiologic riot call to the adrenal gland to mobilize the defensive forces of the body; and so the person who is the victim of chronic fears, as in the case of a neurosis is more or less in a constant state of tension all of the time; and the perverted fear soon becomes a tyrannical master over the body giving rise to muscular tremors, palpitation, shortness of breath, epigastric distress, anorexia, constipation, etc. These symptoms in turn attract the attention of the victim and create new fears which then stimulate the adrenal gland all over again to secrete its epinephrine, and so a vicious cycle is set up which is the pathogenesis of a neurosis.

The symptoms of a neurosis exhibit an enormous range of physical and mental manifestations. They may be local or general, and may involve any or all parts of the body. The patient commonly has an anxious expression, his face shows pallor or is flushed, the pupils of his eyes are dilated, his muscles may be tense, the tonus of his body is increased, he does not relax well, his hands and feet are blanched and cold and sometimes cyanotic, his reflexes are frequently exaggerated; he manifests all manner of visceral symptoms, as disturbances in the appetite, constipation or diarrhea, coated tongue, epigastric distress, palpitation, polyuria, sweating palms, etc.

Between the more acute spells, the patient manifests mental depression, vague fears, chronic fatigue, insomnia, loss of weight and other visceral symptoms. Mentally he is generally pessimistic, irritable, unhappy and given to worry.

Sometimes the entire syndrome of a neurosis centers upon a particular organ or group of organs producing a definite syndrome referable to that system. The commonest focal point of a neurosis is the digestive tract. The patients with digestive neurosis are sometimes spoken of as having barometric abdomens, signifying that their emotions are expressed in their abdomens. Among the symptoms encountered are: loss of appetite, anorexia, coated tongue, dry mouth, bitter taste, epigastric distress, heart burn, lump in the pit of the stomach, fullness after meals, vague or localized abdominal pains, constipation or diarrhea or the two alternating, mucous colitis, etc. Their reaction to foods at times indicates a hyperacidity, or a hypoacidity, or at times it follows no known law of physiology. Thus beef is tolerated, but veal causes distress; white bread is acceptable, but a cereal made of the same flour causes a lump in the pit of the stomach. Even if we allow for the occurrence of allergic reactions, there still remains numerous inconsistencies for which there seems to be no adequate explanation beyond the bizarre manifestation of the neurosis. These digestive symptoms may simulate the syndrome of gastric irritation, irritable colon, or peptic ulcer. The pain and distress that the

neurotic complains of seems to be out of all proportion to the functional derangement found on examination. The neurotic suffers more with his functional disorder than the stabilized person does with his organic disease. The nervous person is frequently hypersensitive to pain. At times his persistent complaints makes the differential diagnosis between functional and organic disease difficult. Alvarez has pointed out that today many a half crazy woman gets herself operated on time after time simply because she insists that the queer symptoms in her abdomen are due to intestinal obstruction which must be relieved at once if her brain is not to be destroyed by the toxins arising in the stagnating intestinal contents. Likewise other patients get all of their teeth extracted because of their persistent complaint of tingling distress or pain in their mouths.

The system next commonly involved is the circulatory system in which occur pallor, blushing, tachycardia, palpitation, anginal pain, cardiac arrhythmia, fear of impending death, shortness of breath, chest pains, etc. Genitourinary symptoms are common as polyuria, dysuria, impotence, dysmenorrhea, frigidity, amenorrhea, etc. Vasomotor symptoms occur as sweating, cold extremities, cyanosis, moist palms, blushing, pallor; also general symptoms as fatigue, loss of weight, secondary anemia, malnutrition, etc.

Among the common mental and nervous symptoms are worry, fear, apprehension, giddiness, tinnitus. Insomnia is an annoying symptom manifested by trouble in getting to sleep, broken sleep, or being awakened at a premature hour. Impaired memory and inability to concentrate are common, shyness and a feeling of inadequacy or inferiority may develop as well as numerous groundless fears and phobias.

Worry is one of the distressing symptoms of neurosis. Worry is an expression of fear, usually chronic in nature. It is considered to be an end product of prolonged thwarting and frustration, in which the conflict may take place within the conscious or the subconscious domain of the intellect. A mild degree of worry is to be considered normal, but worry out of proportion to the existing jeopardy is abnormal. Worry produces visceral symptoms which then give rise to cause for further worry, and so a vicious cycle is produced. Worry unfortunately is not a self limited disease, it does not tend to cure itself. It is the antithesis of creative effort, it is a destroyer of energy and a waster of time.

The direct diagnosis of a neurosis is made upon the presence of positive evidence and not upon the absence of organic disease; also it must be differentiated from those organic diseases it tends to resemble; third it must be differentiated from the psychoses because of the marked difference in the prognosis; and lastly it must be evaluated quantitatively as it may be superimposed upon an organic disease.

Ross gives the following criteria for making a direct diagnosis of a neurosis; (1) the peculiar and often contradictory nature of the symptoms, their illnesses do not run the usual clinical course, (2) the presence of nervous symptoms as anxiety, apprehension, panics, phobias, etc., (3) the attitude of the patient towards

his disease, he is inclined to emphasize the severity and magnitude of the aches and pains that he is subject to, and (4) the whole life history in which are found repeated examples of his neurotic tendencies.

Neuroses tend to resemble certain organic diseases and must be differentiated from them. For example an anxiety neurosis may simulate an early hyperthyroidism or a tuberculosis or a cardiovascular disease. A gastric neurosis may resemble a peptic ulcer or a gastric malignancy. Other instances may be cited. Obviously these and other organic diseases must be excluded by careful physical and laboratory examinations.

The differential diagnosis between a neurosis and a psychosis has to be considered, but this is beyond the scope of this paper.

Last and perhaps the most difficult phase of the differential diagnosis is the quantitative evaluation of the neuroses since neuroses frequently accompany organic disease. Thus a patient may have gallstones, but if he examines his coated tongue every hour in the day he has a neurosis as well. A patient has a mitral regurgitation but if he feels his pulse every hour he also is a neurotic; a patient with lues considers himself a pariah, he is a neurotic as well as a luetic, etc.

The treatment of a neurosis begins properly in early life when the child should be taught to meet the rebuffs of life with poise and avoid expressing his frustrations in tantrums, moods or emotional outbursts. Unfortunately most of us catch the neurotic patient in adult life when his habits are already set, and his reactions to social problems have already become an integral part of his general behavior pattern.

Nevertheless much can be done for the neurotic patient; but the degree of therapeutic success depends entirely on the skill of the physician. To tell a neurotic patient that he is a bundle of nerves and to go home and forget his troubles is merely to admit one's inability to cope with a trying situation and to condemn the victim of a neurosis to continue his search for aid. The neurotic is earnestly seeking relief from his symptoms in whose reality he is firmly convinced; but strangely enough he may want to keep his neurosis; thus presenting a paradoxical situation in which he seeks relief from his aches and pains but desires to retain his "certificate of illness." There is probably no branch of medicine that requires greater patience on the part of the physician than the treatment of a neurosis.

A neurosis is primarily a psychogenic problem, yet there are many symptoms which dominate the picture

and which require immediate attention. In general there are three therapeutic approaches to a neurosis, namely psychotherapy, symptomatic treatment and physical therapy. Each of these has its own uses in the concerted attack on the neurosis.

In the beginning of the treatment it is often desirable to use drugs to control symptoms or allay the anxiety of the patient; particularly the sedatives as phenobarbital or the bromides; bland diets are generally indicated, and the vitamins are useful for those requiring them. This symptomatic treatment gives immediate relief from the distressing symptoms and attacks the vicious cycle at a vulnerable point, also it does much to encourage the neurotic to place confidence in his physician and thus prepares the way for psychotherapy. Physical therapy likewise tends to relieve the symptoms and is in itself a powerful psychotherapeutic agent.

The technique of psychotherapy is largely a personal routine with the physician. Unfortunately for psychotherapy it became clouded in an atmosphere of mysticism and black magic in the past. There is no need of surrounding psychotherapy with a nebula of mysticism. Psychotherapy can be simple and direct. Indeed many physicians and healers are excellent psychotherapists without being consciously aware of it.

Psychotherapy begins with the physician himself. He must remember that the neurotic in the first place wants an audience, so he must be a good listener. The neurotic feels that he is a neglected person, so the physician must be sympathetic. The patient believes that his symptoms are real and often painful, the physician must not belittle them. The patient usually suffers from a feeling of inadequacy or instability, so the physician must present a firm and positive program about which the patient can build a constructive program of living.

Such a program is time consuming, but it is the price the physician must pay if results are to be obtained.

The prognosis of a neurosis is necessarily guarded since the underlying causes are ever present. Nevertheless, the average neurotic can be materially helped and made symptom free for years at a time. Some groups present an unfavorable prognosis: namely those who desire to profit from their "certificate of illness," those who use it as a defense mechanism against the realities of life, those suffering from psychoses; in these the prognosis is less favorable.

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Dysentery in American Troops in the Middle East *

By

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DYSENTERY has proven a major problem in all wars in which we have a record of the medical history. One of the most striking examples of this was in the Gallipoli Campaign during World War I. Similarly in this war dysentery exists in both Allied (1) and Axis troops, (2) (3) but it is only recently that American troops have been in endemic areas in sufficient numbers and for a sufficient length of time to permit some evaluation of this problem among them.

The purpose of this report is to discuss the incidence, type, diagnosis, symptoms, and treatment of dysentery in American troops as it was observed in a general hospital in the Middle East. The report is made with full knowledge that war time conditions have imposed certain limitations on the completeness of some phases of the work.

From January to August, an eight month period of this year, we have examined and cultured 1298 stools in the laboratory of this hospital. All specimens were examined grossly and a particular search made for mucus and blood; direct microscopic as well as concentration methods and fixation and staining of smears were employed in searching for parasites. The method of culturing was that usually carried out in bacteriology laboratories to investigate the biochemical and antigenic reactions of dysentery organisms. A portion of the stool, particularly that containing mucus, was inoculated simultaneously on nutrient broth, selenite broth and on a plate of differential media. The latter consisted of either desoxycholate citrate agar or eosin-methylene blue agar. The selenite broth in addition to its value in isolating typhoid-paratyphoid organisms was found particularly helpful for replating, if the original plate growth was too heavy, or too scant. Pathogen colonies on the desoxycholate citrate agar or eosin-methylene-blue were about one to two millimeters in diameter, gray-white, flat, smooth, clear, and glistening. Characteristic colonies are discrete, do not spread and colonies of *B. coli* are usually scattered among the pathogens. Colonies of this type were picked and inoculated on a slant of Russel's double sugar, or Kligler's iron. The latter proved preferable because it demonstrated the production of H_2S . After 24 hours incubation a set of seven sugars were inoculated from the growth on those tubes showing the typical acid butt and alkaline slant. The sugars employed were glucose, lactose, saccharose, maltose, mannite, xylose, and dulcitol. After the type of pathogen was determined by

the fermentation reaction, agglutination was carried out with the type-specific antiserum where available. The Flexner antiserum was polyvalent and contained the V. W. X. Y. and Z. types. The only salmonella antisera available was for *S. paratyphi*, *S. Schottmuelleri*, and *S. Hirschfeldii*. The antisera for the *S. Paratyphenteriae* (Boyd 88) and for *S. Morgani* we prepared ourselves. The organisms were set up against dilutions of antiserum ranging from 1-20 to 1-640, incubated in the water-bath at 55° C. for 24 hours and then placed in the ice-box for an additional 12 hours. Agglutination was read microscopically at the end of this time.

From the total number of stools examined we selected 300 as a control or base line group. Two hundred of these were American soldiers classified as food-handlers, fifty were Sudanese soldiers and fifty were native workmen. For the purpose of this study all were assumed to be normal, male adults representative of the group from which they came. The incidence of parasitic infestation was low in the food-handler group; two men were found to harbor the ova of *ascaris lumbricoides*. Two of the Sudanese, likewise, showed ova in the stool; in one an *ascaris lumbricoides* and in the other a *stercoralis strongyloides* was found. In marked contrast to these were the findings in the stools of the native workmen; 98% showed from one to three of the parasites listed in Table I in either the vegetative or ova form.

TABLE I.

Parasites Found in Stools of Native Workmen

1. *Ascaris lumbricoides*
2. *Trichomonis hominis*
3. *Strongyloides stercoralis*
4. *Ankylostoma duodenale*
5. *Shistosoma hematobium*
6. *Endamoeba histolytica*
7. *Giardia lamblia*
8. *Trichostrongylus columbiformis*

The carrier rate of bacillary dysentery organisms in the food-handlers was 1.5% and in the Sudanese and native workmen 4%. *S. paratyphenteriae* Flexner and Newcastle, and *Salmonella enteritidis* and *S. Morgani* were the types of organisms isolated.

In an attempt to further evaluate the potential sources of food contamination on the post a culture of flies and the hands of food-handlers was made. To do this a number of flies were killed in each of the mess halls and in several rooms of the laboratory where various sources of contamination were thought likely. The

flies from these six sources were macerated and cultured in the manner followed for stools. In each instance a *B. Coli* was recovered and in two instances a *B. Fecalis Alkaligenes* was found.

To culture the hands of the food-handlers a sterile swab prepared in nutrient broth was passed beneath the nail of each finger of the right hand. This procedure was carried out on fifty food-handlers without previous warnings and while they were at work. A culture positive for *B. Fecalis Alkaligenes* was obtained from four of the fifty subjects.

The significance of the study of this control group suggests that the American soldier classified as a food-handler on this post does not show a high carrier rate for bacillary dysentery organisms or parasites in his stool. The native workman likewise shows a low carrier rate for bacillary dysentery organisms, but an exceedingly high one for parasites of both the pathogenic and non-pathogenic types. The lowered carrier rate for parasites in the Sudanese, who is also an African native may be due to the hygiene resulting from army supervision. The results of the cultures of flies and the hands of food-handlers again emphasizes that this is a potential source of food contamination.

All of the stool specimens not in the control group were obtained from patients in the hospital or in the dispensary. Among these patients 116 were found infested with an intestinal parasite; some harbored simultaneously as many as three of the types listed in Table II.

TABLE II.

<i>Parasites Found in the Stools of Patients</i>	
1. <i>Trichomonis hominis</i>	86
2. <i>Entamoeba histolytica</i>	9
3. <i>Giardia Lamblia</i>	8
4. <i>Chilomastix mesnili</i>	3
5. <i>Ascaris lumbricoides</i>	3
6. <i>Ankylostoma duodenale</i>	5
7. <i>Endolimax nana</i>	1
8. <i>Enterobius vermicularis</i>	1

The non-pathogenic variety of parasite was found in the majority of these patients and as would be expected the symptoms were comparably mild. However, nine patients had an *Entamoeba Histolytica* infestation of an acute nature and in 8 instances there was an associated fever, malaise, abdominal cramps, and diarrhea. In one patient motile amoeba were found with a complete absence of dysentery symptoms; the chief complaints on admission were malaise and low back pain. The incidence of the non-pathogenic parasitic infestations showed a striking seasonal variation. The great increase in cases occurred during the latter part of June and early part of July. The *Entamoeba Histolytica* infestations occurred sporadically but it was noted that this type of infestation did not occur in our own hospital personnel until we had been in the Middle East about six months or longer.

From a culture of the patients' stools 238 were found to harbor a bacillary pathogen. The type of pathogen as well as the number of stools cultured showed a seasonal variation. During the month of July

almost half as many stools were examined as during the entire preceding six months. The concomitant increase in flies at this time makes the view tenable that they are one of the important transmitters of bacillary dysentery organisms. The predominant organism causing bacillary dysentery in this region is undoubtedly the *B. paradysenteriae* Flexner, and during the six months from January until the end of June of this year 60% of the pathogens isolated were of the Flexner type. During both periods the balance of pathogens was made up of *Salmonella* and para-dysentery organisms.

TABLE III

<i>Incidence of Bacillary Pathogens Isolated from Dysentery Stools</i>	
Sh. Flexner	53%
S. Enteritidis	11%
S. Morgani	9%
Sh. Paradysenteriae Boyd 88	7.5%
S. Schottmuelleri	5.5%
Sh. Schmitz	4%
Sh. Dysenteriae	3%
Sh. Sonne	3%
Sh. Manchester	2%
S. Paratyphi	1%
Sh. Hiss	0.5%
Sh. Paradysenteriac Boyd 170.....	0.5%

The symptoms of those patients with the Flexner and Shiga infections were characteristic of bacillary dysentery, i.e., they consisted predominantly of fever, malaise, abdominal cramps, and diarrhea. The average high temperature was 100.8° F. the frequency of stool averaged 11 in 24 hours, and the average length of hospitalization was 10 days. Approximately 60% of the stools were found to contain mucus or blood, or both. The blood count showed no variation except that the total white count was elevated to 10,000 or 11,000 in few cases. There were no pronounced urinary changes observed. The symptoms of the patients suffering with a *Salmonella* or other type of paradysentery infection were similar, but on the whole somewhat milder than those described above. Actually few of the patients out of the entire group discussed here were seriously ill; neurotoxic and cerebrotoxic symptoms were infrequent; they occurred almost exclusively in the patients with paratyphoid or *Shigella*-dysenteriae infections. Following is a case history representative of the group in whom a specific bacillary dysentery organism was isolated as well as one representative of the group in whom stool cultures were negative.

CASE No. 1 NON-SPECIFIC DIARRHEA

R. T. M., T/4th Med. Detach. age 22, 1 3/12 yrs. military service; 10/12 year service in the Middle East. The family and past personal history have no bearing on the present report. The illness began 27 Aug. when generalized achiness, malaise and nasopharyngeal congestion which persisted until 29 Aug. when generalized abdominal pain and diarrhea began, the latter averaging 10 per 24 hour period. On 30 Aug. he was hospitalized at which time the oral tem-

perature was 37.7° C. (100° F.), pulse 110, respirations 20 per minute; the naso-pharynx was congested; there was marked tenderness over the sigmoid colon; the examination was otherwise essentially normal. Complete blood count and urinalysis were normal. The blood Kahn was negative. At the end of 24 hours the temperature was 36.9° C. (98.4°), pulse 92 and respirations 18. There were 8 stools in the 24 hour period. During the second 24 hours the temperature remained normal and there were three semi-formed stools. The stool culture showed no pathogenic organisms at the end of 48 hours. The convalescence was uneventful and he was discharged to duty at the end of the fifth day of hospitalization, with final diagnosis of Acute Catarrhal Enterocolitis, cause undetermined.

CASE 2 BACILLARY DYSENTERY

M. R. R., 2nd Lt. A.N.C. Age 29, 1 yr. service; 9/12 year service in Middle East. The family history was irrelevant. The only event in the past history concerned with the present discussion was the occurrence of a mild attack of diarrhea in Nov., 1942 which persisted for three days and ceased spontaneously. The present illness began with malaise and a temperature elevation to 38.8° C. (102° F.) the afternoon of 21 June, 1943. The temperature was normal in the evening, the malaise persisting. The following day the temperature rose to 40.0° C. (104° F.) chilly sensations occurred and the patient was hospitalized. At the time of admission the temperature was 39.6° C. (103.4° F.) pulse 134 and respirations 28 per minute. She was toxic, disoriented, and dehydrated. The examination was otherwise normal. The erythrocyte count was 5,410,000; the leucocyte count was 7,500; 30% segmented and 49% non-segmented neutrophils, 11% lymphocytes, 6% eosinophils and 1% basophils. The urinalysis was normal; no malaria parasites were found. Symptomatic treatment was instituted. The irrationality increased during the night. The day following admission nausea, vomiting and diarrhea developed, the stools contained mucus, pus, and blood and 20 liquid movements occurred during the 24 hour period. The temperature remained elevated between 38.8° C. and 40.0° C. (102-104° F.). On 24 June a pathogenic organism was reported in the feces culture, the type not yet determined. Sulfaguanidine was begun in the dosage described in this article. She remained irrational, was able to tolerate fluids orally and had 12 liquid stools during this third 24 hour period. The temperature gradually descended reaching 37.2° C. (99° F.) the evening of 24 June. The blood culture at the end of 48 hours was negative, but stool culture was positive for *Sh. paradysenteriae* Flexner. On 25 June the temperature remained normal and the patient was hydrated and rational and had 2 liquid stools during the 24 hour period. From this time on convalescence was uneventful. Sulfaguanidine was stopped on the 8th day of the disease after a total of 112 Gms had been given. The patient was transferred to quarters on the 10th day and discharged to duty the 14th day after onset of illness with a final diagnosis of dysentery, bacillary, acute, due to *B. paradysenteriae* Flexner.

All of the patients responded favorably to treatment

and with the exception of some who were being treated for a condition other than dysentery, were discharged well. All in whom a pathogen was isolated, except those with a paratyphoid infection, were treated with chemotherapy; in the majority sulfaguanidine was given, but in a small number sulfathiazole was used. Later two patients with a paratyphoid fever (*S. Schottmuelleri*) were given sulfaguanidine but there was no amelioration of symptoms and the stool culture was still positive two weeks after the therapy was terminated.

From an observation of this group of patients it would appear from the sporadic and constant occurrence of this disease that we are dealing with endemic dysentery. This coincides with the type of infection that might be anticipated for this region(4) as well as with the experience of troops in the central European theatre of war. Since we are not dealing with epidemic proportions of this disease and the fact that the majority received chemotherapy early may account in large part for the relatively mild course in the group as a whole.

Out of all the patients in whom a stool specimen was cultured there were 300 in whom a pathogen was not recovered. However, an analysis of these patients' symptoms showed that the majority did not have true dysentery. Most of these patients were admitted to the hospital suffering from an upper respiratory infection, biliary tract disturbance, gastro-duodenal ulceration or gastro-intestinal neurosis and symptoms of fever, malaise, prostration, abdominal cramps, and diarrhea existed in only about 10%.

Additional stool specimens were collected on patients with symptoms of this severity so that culture and the search for parasites could be carried out several times. In addition if any ulceration or erosion of the bowel mucosa was noted on proctoscopic examination, saline washings were also examined for parasites and ova. Although these procedures rarely demonstrated a pathogen that was not found on the original examination, the majority showed improvement when treated with sulfaguanidine.

A particular interest was taken in this group of patients because it is felt that they fall into a class often referred to in this region as "Gypy Tummy". This term has no scientific significance but as a lay term it is applied to any and all forms of diarrhea and dysentery irrespective of the severity of the condition and as such has gained wide usage. The one feature of "Gypy Tummy" that is agreed upon by most military medical personnel is that the cause is unknown and that examination and culture of the stool fails to reveal a pathogen. From our own observation of patients admitted to the hospital with this diagnosis we have assumed that the condition might be defined as one wherein the patient has fever, malaise, prostration, abdominal cramps, and diarrhea. These symptoms persist for 48 to 96 hours and then disappear with only symptomatic or no treatment at all. Recurrence is common at intervals varying from weeks to months. It is felt that it is fallacious to consider this condition peculiar to this region or an entity of unknown cause.

for the following reasons. Firstly it is not unusual to recover a pathogen(5)(6) on stool culture in a varying percentage of bacillary dysentery patients, secondly, if an adequate study is carried out a pathogen will be found in the majority of bacillary dysentery patients, and thirdly the similarity in both the symptoms and the chemotherapeutic effects to those patients harboring dysentery bacilli points strongly to the latter or related pathogens being the causative agent.

The importance of analysing this lay term is primarily to combat the erroneous conceptions to which it has led. A distinction has been drawn between dysentery and "Gypy Tummy", wherein the former is considered a bona fide disease that requires medical attention and treatment, but the latter is looked upon as a mild disorder of mysterious origin which everyone must inevitably, sooner or later, acquire in this region. In addition medical investigation and treatment is thought unimportant and unnecessary. Our experience indicates that such a view is incorrect and the longer it is held the longer will be the number of individuals with subacute dysentery who will remain ambulatory and untreated. Ultimately a certain number of these will develop chronic amebiasis and sequellae of chronic amoebic or bacillary dysentery. Probably one of the most important means of preventing such development would be the entire elimination of the use of the term "Gypy Tummy", as well as the attitude of mind it has created and have greater emphasis placed on specific dysenteries associated with mild symptoms.

SUMMARY

A report is made on the examination and culture of 1298 stool specimens in a general hospital for American troops in the Middle East. Three hundred of these were selected as a control group and showed that the American soldier classified as a food-handler did not have a high carrier rate for either amoeba or bacillary dysentery organisms. The native workman in this region does not have a high carrier rate for bacillary dysentery, but shows some form of intestinal parasitic infestation in almost 100% of the cases.

Approximately twelve per cent of the patients examined harbored one or more forms of intestinal parasite; 23% showed a bacillary pathogen in the stool. The predominant pathogen was the *B. paradysenteriae* Flexner, which showed considerable seasonal variation in incidence. All of the patients were treated with sulfaguanidine or sulfathiazole and all made a satisfactory recovery. The fact that few of these patients were seriously ill is probably due in part to the early administration of chemotherapy and the lack of epidemic proportions of the disease. The latter is attributable to the high standard of hygiene maintained on the post. Of all the patients from whom a pathogen was not recovered from the stool, only 10% had symptoms exclusively attributable to dysentery. It is felt that such patients should not be classified as having "Gypy Tummy". The term "Gypy Tummy" should be entirely eliminated and emphasis placed on the dysentery with mild symptoms.

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Chronic Constipation*

By

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FOR some years I have emphasized the evident need for the recognition of physiologic standards in Gastro-Enterology. The recent literature on the subject of constipation displays a lack of comprehension of the underlying fundamentals of gastro-intestinal motility.

Recent advances in the physiology of digestion, particularly the work of Cannon (1) Carlson (2) and Alvarez (3) add emphasis to the role that motor disturbances play in the production of gastro-intestinal symptomatology. Cannon (4) as well as Meltzer (5) has shown that the gastro-intestinal movements occur in a definite orderly fashion. The work of Alvarez (6) reveals a gradient of irritability from cardia to pylorus. He suggests that the entire gastro-intestinal tube may

have been originally so constructed that the rhythmicity of any one segment varied inversely as the distance from the pharynx. We are, therefore, justified in visualizing the gastro-intestinal tract as a beautiful mechanism whose motor apparatus functions in a rhythmic, orderly fashion, concomitant with appropriate, specific chemical changes.

The disturbances in colonic motility are of special interest. Hurst (7) fixes a physiologic standard for normal defecation, asserting that the colon in normal, healthy young adults should be emptied from the splenic flexure to the anus. The work of Hurst and W. J. Mayo (8) on the anatomy and physiology of the recto-sigmoid apparatus discloses a definite mechanism comparable to the ileocecal valve and cardia. They

demonstrate that the column of fecal matter is held at the recto-sigmoid angle until the time for defecation occurs. Under normal conditions the rectum is free from fecal matter, except during the act of defecation. Using the foregoing standards, I reported a large percentage of patients who presented themselves for treatment for constipation, who in reality exhibited no colonic stasis, but were suffering from the effects of habitual use of cathartics and enemas. To restore normal function in these patients all that was necessary was to permit the intact colonic mechanism to perform its work unimpeded by drugs or enemas.

When one opens the lower colon of any healthy vertebrate, including man, one will find formed, dessicated fecal matter. It is obvious that restoration of function can not consist in changing the contents from dry to a liquid state by the habitual use of drugs and enemas. Unfortunately a large number of physicians are still obsessed with the notion that the human colon is a sewer that should be kept continuously "flushed out." Carlson says, "Auerbach's plexus is the brain of the intestine." It is a brain much older and better organized than that of man, who lightly attempts to interfere with a biologic function established in all forms of life throughout the ages. Abdominal or colonic massage is absurd. Who has the presumption to state at what time the intestinal contents should move forward? It is our duty to attempt restoration of normal rhythm instead of using methods that tend toward further disorganization.

It is possible for constipation to be produced by motor insufficiency of the stomach or small intestines. For the angulations and adhesive bands that involve the terminal ileum, surgery is, of course, indicated. The treatment of chronic constipation in reality resolves itself into a consideration of the restoration of colonic function.

ANATOMICAL CONSIDERATIONS

The iliac colon extends from the crest of the ilium to the inner border of the left psoas muscle. It is the only portion of the lower colon that is always accessible to palpation. The pelvic colon forms a freely movable loop, varying in length from 5 to 33 inches, the average length being about 17 inches. It has no constant position, but in its most typical arrangement passes from the termination of the iliac colon at the inner border of the left psoas muscle, loops to the right, and ends in front of the third sacral vertebra, where its junction with the rectum forms the pelvi-rectal flexure.* The rectum is between four and five inches in length and lies in contact with the sacrum and coccyx. At its termination the rectum bends slightly backwards and merges into the anal canal. The anal canal, about 1 to 1¼ inches in length, is directed downwards and backwards, forming almost a right angle with the rectum. It forms a narrow canal with longitudinal folds of mucous membrane, surrounded by the muscle fibers that form the external and internal sphincter apparatus.

The usual description above applies very well to the average normal subject as the organs appear at autopsy. In the living individual the anatomical relationships are not constant, but vary with the structure or bodily

habitus of the individual.

Mills (9) in his work on habitus, has demonstrated that the visceral contents of the abdominal cavity conform to certain definitely recognizable anatomic types. The most striking variation is shown in the difference in the position and form of the stomach. Mention may be made here of the long, narrow fish-hook-formed stomach of the asthenic, extending to the pelvis, in contradistinction to the almost transverse high stomach of the hypersthenic.

The colon also shows very marked variations corresponding to the bodily habitus of the individual. In the hypersthenic, the sigmoid loop or pelvic colon is high above the pelvic cavity and really presents but one curve almost circular in character. In the asthenic, the loop is more markedly S-shaped and is contained partly in the pelvis. In the asthenic, a portion of the transverse colon and the pelvic colon are massed together in the pelvic cavity. In each instance the position assumed by the colon corresponds to its particular anatomic type, and is not to be considered as pathological. Therefore, from a clinical standpoint, the consideration of the form and position of the lower colon presents, *a priori*, a very pertinent question, namely, does the colon conform to the bodily habitus, or is there a variation from the individual's anatomic type? For example: the pelvic colon of the asthenic may be pushed out of the pelvis by a tumor mass, or the hypersthenic colon may be tied down in the pelvic cavity by inflammatory processes.

The rectum, also, while immovably fixed, shows certain variations corresponding to the habitus. In the asthenic type, the anal canal is short, located near the coccyx, and the proctoscope enters at once into a large capacious ampulla. In the hypersthenic individual the anal canal is much longer, situated further from the lower spine, and proctoscopy reveals a relatively much smaller ampulla. In many hypersthenic individuals I found by actual proctoscopic measurement (the patient in the knee-shoulder position), that the anal canal was from 2 to 2½ inches in length, while that of the asthenics varied from 1 to 1½ inches in length.

The variation in form, observable in the different anatomic types, is not more striking than the differences exhibited in function. In this connection one may mention the evident tonicity of the colon in the hypersthenic as compared with the extreme "atony" of the asthenic colon. The rate of motility is high in the hypersthenic, low in the asthenic, intermediate in the sthenic. It may be physiological for the hypersthenic to defecate two or three times daily, while in the asthenic the rate may be normally so low as to permit an evacuation but once in two days. The intestinal tube of the sthenic and hypersthenic is well adapted to the high energy requirements of individuals exhibiting this structural type. On the contrary, the intestinal tube of the asthenic, with its hypotonic character, low position and slow rate of motility, places the asthenic individual at a disadvantage in the machinery required for the production of bodily energy.

A predilection for the development of certain pathological conditions may be associated with habitus, e.g.,

the asthenic is notably predisposed to colonic stasis and more frequently presents the syndrome, which is usually termed "autointoxication." Moreover, the pelvic colon, from its low position, is more likely to become involved in pelvic inflammatory processes. On the other hand, the condition known as diverticulosis occurs more frequently in hypersthenics and sthenics.

William J. Mayo made a very careful study of the recto-sigmoid apparatus. He has shown that it consists "of $3\frac{1}{2}$ inches of the intestinal tract, which includes the terminal 2 inches of the sigmoid and the proximal $1\frac{1}{2}$ inches of the rectum. It is the narrowest part of the large intestine, and is more often the location of pathological processes than any part of the gastro-intestinal tract excepting the stomach and duodenum." Mayo's study is based upon dissections in 46 cadavers. The terminal sigmoid contracture was found in 80 per cent of cases examined. Mayo has shown that the recto-sigmoid apparatus is controlled by the pelvic plexus of nerves, which is made up of variable number of sympathetic ganglia joined from above by spinal nerves from the lumbar region, and from below by the spinal nerves from the sacral region.

Langley (10) and others have shown that nerves derived through the hypogastric plexus are inhibitory in character, while those from the spinal and sacral nerves produce contracture of the muscle-fibers of the intestine upon stimulation.

Keith (11) has shown that the smooth muscle-fibers in this region have the power of originating contraction, and that impulses are collected in certain neuromuscular nodes and correlated.

Mayo and Hurst both are of the opinion that the failure of co-ordination in early life results in the so-called idiopathic dilatation of the colon, or Hirschsprung's disease. This disease is, therefore, according to Mayo, similar in origin to cardiospasm at the cardiac orifice and ileocecal valve stasis. Hurst (12) has suggested the name of pelvirectal achalasia instead of Hirschsprung's disease. According to Hurst, the active relaxation of the circular muscle-fibers at the pelvi-rectal juncture fails to occur, and a spasm is originated which leads to partial obstruction, with consequent dilatation and hypertrophy of the pelvic colon. The colon, when once dilated, produces a kink by overhanging the undilated portion below, thus producing increased difficulty in defecation, progressive accumulation of fecal matter and progressive dilatation and hypertrophy of the muscle-fibers of the colon, finally resulting in broken compensation, with the loss of peristaltic power.

PHYSIOLOGY

Mayo's anatomical studies have led him to the conclusion that the recto-sigmoid apparatus is a definite mechanism, which retards the fecal current and prevents continuous progress of the intestinal contents into the rectum. Hurst, who examined a large number of young adults, comes to the same conclusion; he further states that normally the rectum does not contain fecal matter, except during the act of defecation. At other times the fecal column is prevented from entering the rectum by the tonicity of the recto-sigmoid apparatus.

The studies of Hurst, Holzkecht (13) Barclay, (14) Case (15) and others disclose that the colon is emptied by a series of mass movements. When the fecal column, which has been held up at the recto-pelvic juncture, enters the rectum, the desire to defecate is provoked. As Hurst has shown, this desire is not due to stimulation of sensory nerves, inasmuch as they are absent in the rectum, except in the mucosa of the anal canal. The reflex is established by means of the "muscle sense" of the distended rectum. The first mass movement empties the rectum and part of the pelvic colon. Secondary mass movements occur and continue until, under normal conditions, the entire large intestine below the splenic flexure is completely emptied. Hurst has demonstrated that about 33 hours' time is required for a meal to be entirely evacuated from the gastro-intestinal tract. Food taken nine hours before the act of defecation should reach the splenic flexure and part of it appear in the feces. These figures represent the time required for the average healthy individual at active muscular work. Modifications must, of course, be made for the asthenic type who habitually have a slower rate of colonic motility, as well as the hypersthenic whose motility is higher than the average individual, as pointed out by Mills in his work on habitus.

While roentgen-ray examination is the best means to determine colonic motility, simpler tests are available, e.g., a 5-gr. carmine capsule, given one before and one after the evening meal. The color should appear (traces at least) in the feces evacuated the following morning. The second morning the entire stool should be colored by the carmine. On the third morning there should be no trace of the coloring matter in the feces.

When magnesium sulphate is taken into the stomach, it is partly converted into sodium sulphate and magnesium carbonate, substances which increase the contractile phase of peristalsis, according to Meltzer (16). The remaining unconverted portion of magnesium sulphate stimulates the inhibitory or relaxing phase of peristalsis, thus producing the well-known rush movement of a dose of Epsom salts. Meltzer's definition of tonus is as follows: "The resultant effect of the antagonistic action may be manifest at the same place and at the same time. This is tonus. The degree of character of the tonus depends on the preponderance of one or the other factors."

Goldschmidt and Dayton (17) have shown that the colonic wall is impervious to the passage of magnesium sulphate or sodium sulphate; therefore, there can be no possible danger in using these salts in the bowel. They have demonstrated that hypertonic solutions of these salts increase in volume and decrease in concentration approaching the blood level. Solution of concentration nearly iso-osmotic with the blood show little change in volume. Hence there is free passage of water with no diffusion of the sulphates. Sodium chloride solutions, on the other hand, diffuse freely from gut to blood and vice versa. In cases of extreme "atony" I used sodium sulphate and found it produced painful contractures without much result in producing defecation. Equal parts of a 25 per cent solution of

magnesium sulphate and sodium sulphate have, on the other hand, given us very remarkable results in producing defecation in many cases of hypotonic states of the recto-sigmoid apparatus, pelvic and iliac colon.

TREATMENT OF SIMPLE UNCOMPLICATED CONSTIPATION

The patient must be instructed in the rudiments of colonic physiology. Enemas and all purgatives must be stopped at once. The fecal column should be permitted to form in the lower colon. It will require about three days' time for this to occur. Patients who are apprehensive of disaster must be reassured, nothing will happen even if the bowels do not act. On the morning of the third day the proctoscope is introduced and the sphincter dilated, always making pressure with the instrument upward toward the spine, with the patient in the knee chest posture.

A pint of cold water should be taken upon arising, followed at once by fifteen minutes of active exercises directed to involve the abdominal muscles. Defecation should follow immediately after breakfast, allowing sufficient time for the act to be complete; *strong intermittent pressure with the hands over the left side of the abdomen* is of great aid in evacuating the contents of the lower colon. The diet should be rich in whole wheat bread and cereals, as well as vegetables and fruits.

The *oil retention enema* is of great value in the treatment of spastic conditions of the colon. Six ounces of mineral oil is introduced at bedtime and allowed to

remain in the colon all night. I have demonstrated by x-ray films (adding bi-smuth to the oil) that reverse peristalsis soon carries it to the caecum. Mineral oil is preferred to the cottonseed and olive oil, inasmuch as no bacteria will grow in its presence.

A course of treatments will definitely cure many cases of colonic diverticulosis. It is of great value in the treatment of ulcerative conditions of the colon. I have recently achieved splendid results in ulcerative colitis.

A remarkable cure resulted after one year's treatment in a case of tuberculous ulcers of the rectum and sigmoid colon: Sigmoidoscopy reveals the ulcer scars with complete disappearance of the tubercle bacilli, after many microscopic examinations of the direct smear; Recurrence of the ulceration is of course apprehended and the patient continues to employ the daily oil retention enema.

The oral administration of mineral oil is not advisable inasmuch as its presence in the small intestine may prevent the absorption of Vitamin A and other vital food elements.

The severe type of hypotonic colon requires some sort of stimulant. The extract of cascara sagrada, from 10 to 30 drops given before each meal is very effective; the patient learns to regulate the proper dosage. Cascara will produce a pigmentation of the mucous membrane of the colon, but no serious injury results from its employment. Phenolphthalein is a drug that produces severe irritation of the mucous membrane of the colon, and is the etiologic factor in many cases of catarrhal colitis.

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Constipation: Further Clinical Evidence of the Use of Bran as a Dietary Laxative Agent*

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ABOUT a year ago we made a report in the American Journal of Digestive Diseases of a study of the use of bran in 135 patients who were constipated. At that time we concluded that clinically 107 patients were improved, 26 remained unchanged, and 2 became worse on bran. Roentgenologically, 15 patients demonstrated acceleration in cecal emptying time, and 27 showed evidence of acceleration in total emptying time. In general, it was demonstrated that bran administered orally aids bowel activity.

Inasmuch as our report (1943) was the first systematic study of the use of bran in constipation, it seemed desirable to obtain additional evidence of the use of bran as a laxative dietary agent.

The present study entails a clinical and roentgenologic evaluation of the influence of bran on intestinal evacuation in 75 individuals who are constipated. The following types were included in this presentation:

1. Habit (irregularities) 10 patients
2. Diet (indiscretion) 41 "
3. Atonic 4 "
4. Mechanical 11 "

Total 75 patients

Procedure:

Patients undergoing this study were not permitted oral medication or enemas and were observed at regular intervals. Roentgenologically, observations were made of cecal and total emptying time before, during, and after bran administration (Amer. J. of Dig. Diseases, 1943) with barium sulfate.

Results:

A. Clinical:

We studied 75 patients; twenty-three males (Group I) and fifty-two females (Group II). Patients who were clinically improved were divided into Class A, those who remained unchanged, Class B, and those who became worse, Class C. In Table I the clinical observations are presented.

TABLE I

Clinical Observations Made on 75 Patients

Group	No. of patients observed	Sex	Progress by classes		
			A	B	C
I	23	Male	22	1	0
II	52	Female	45	6	1
Totals	75		67	7	1

The results recorded in Table I are observations of progress reported to us by the patients; these are confirmed and correlated by roentgenologic studies.

B. Roentgenologic:

In this study particular attention is given to the delay of the total emptying time and the cecal empty-

ing time. The normal average limits are 72 and 96 hours, respectively (Kopstein, 1940). Seventy grams of barium sulfate was used as a water suspension.

Table II shows the number of patients in each group studied roentgenologically.

TABLE II

Roentgenologic Observations Made on 75 Patients

Group	No. of patients observed	Sex	No. of patients showing delayed motility	
			Total time	Cecal time
I	23	Male	16	14
II	52	Female	36	29
Totals	75		52	43

In Table III evidence of improvement, if any, is shown by a comparison (roentgenologically) of the activity of the bowel before and after the bran intake.

TABLE III

Comparative Roentgenologic Study of 75 Patients

Group	No. of patients observed	Sex	No. of patients with delayed cecal time			No. of patients with delayed total time		
			Before	During	After	Before	During	After
I	23	Male	17	14	16	20	16	20
II	52	Female	43	29	40	46	36	45
Totals	75		60	43	56	66	52	65

Discussion:

It was shown in Table I that of 75 patients reviewed, 67 were improved in bowel activity, 7 remained unchanged, and 1 was worse. The subjective findings in Table I were further corroborated by roentgenologic studies—in Table II it is shown that of 75 patients studied, 52 showed delayed total emptying time and 43 showed delayed cecal emptying time.

It is interesting to note that while 66 patients demonstrated delayed total emptying time before bran intake, only 52 showed delay during bran intake, which means that 14 were improved in total emptying time roentgenologically.

We also note that while 60 patients showed delay in cecal emptying time, 43 demonstrated delay while on bran, an improvement in 17 patients.

Therefore, we can say that roentgenologically 31 patients were improved of the 75 patients studied.

Of the 75 patients studied, 67 were improved clinically, and in 31 patients this was verified roentgenologically, or an improvement in 46.2 per cent of the group.

In our previous publication (Streicher and Quirk, 1943) of 135 patients studied, 107 were improved clinically, and 42 patients demonstrated roentgenologic verification, or an improvement in 39.2 per cent of the group.

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* From the Departments of Pharmacology and Therapeutics and Medicine, University of Illinois, College of Medicine, Chicago. Assisted by a grant from the Kellogg Company, Battle Creek, Michigan. Submitted January 6, 1944.

Fat Metabolism*

By

HENRY M. FEINBLATT, M.D.

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THE delayed appearance of increased cholesterol content of the blood after fat ingestion led Bloor (1) to infer that this (cholesterin lecithin) is an intermediate stage of the utilization of fat, a sort of utilization stage such as the change from glycogen to glucose a transport form of carbohydrate.

Meigs (2) found during milk secretion in cows the difference in the lecithin values of the blood plasma before and after the blood has passed the mammary gland sufficient to account for all the fat in the milk which is secreted.

What leads to the storage of enormous amounts of fat in some people and lack of storage in others; to atypical or unilateral deposits? These are problems still unsolved.

London (3) working at Leningrad found higher fat content in the adrenal vein than in the adrenal artery. Because disease of the adrenal was associated with distinct disturbances of fat metabolism, emaciation and secondary gastrointestinal upset following fat ingestion, he felt that the adrenal played a distinct role in fat metabolism.

Cannon (4) suggested that cholesterol may be a waste product of the body and of no further value to it.

In our own metabolic clinic we were impressed by the two opposite groups of cases who fitted into no specific glandular dyscrasia: 1. The obese individual

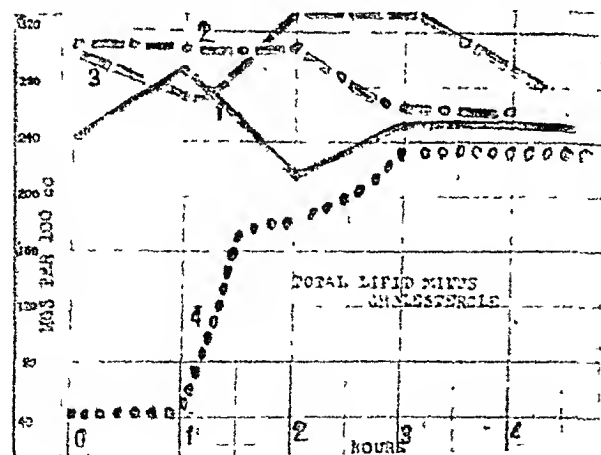


PLATE 1

who was always hungry and specifically craved rich fatty foods and 2. the thin active individual who could not gain weight and who just couldn't enjoy a rich fatty dietary.

Attempts at high fat feedings in these thin individuals were not infrequently followed by spells of vomiting and biliousness. These symptoms did not occur in the obese.

A study was made of these groups in an attempt to determine the mechanism responsible. Twenty-five co-operative individuals, nineteen of the obese and six of the thin type, were selected.

The procedure for the test was as follows: After fifteen hours of fasting, a duodenal tube was introduced into the duodenum. 100 Gm. of fat melted with heat were then introduced into the duodenum through the tube at about the melting point. The fats used were those most commonly employed in the local areas and were standard brands of butter, lard and vegetable fat. Tests with the different fats were done at weekly intervals and the order alternated so that the observations were orderly.

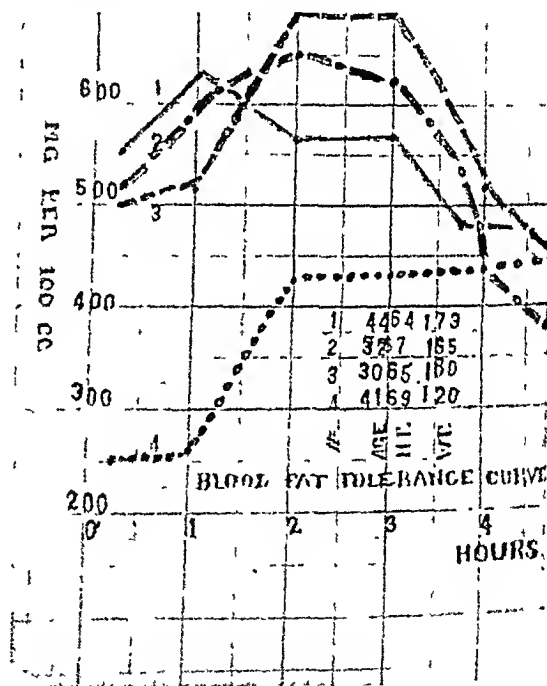


PLATE 2

2 cc. of duodenal contents were then withdrawn from the tube at thirty minute intervals for six to nine hours. Microscopic examination was made of the contents and the fat drops counted with the ordinary hemocytometer. The specimens were studied for their physical character and photomicrographic study made at the various stages of digestion.

Blood was withdrawn by venepuncture every hour for a six hour period. The total blood fat and cholesterol were determined quantitatively and a tolerance curve established.

The duodenal contents of both the obese and thin groups consistently showed almost complete digestion after three hours. There appeared to be the slightest

difference in the degree of digestibility of fats such as lard, vegetable fats and butter. The greatest amount of digestion took place in the duodenum, the fat being refluxed back into the duodenum from the ileum and being continuously mixed with the bile and pancreatic juice.

The blood fat curves of the two groups, however, showed marked variation. In the obese type, there exists a moderate lipemia even after fifteen hours' fast. There is a rising curve following the ingestion of fat, this rise being essentially cholesterol. This process resembles the postprandial rise of glucose following ingestion of starch. Apparently the neutral fat is rapidly taken up by the fat depots. The blood fat level reaches its height within two hours and begins to fall after the third hour.

In the very thin, there is distinct rise in the non-cholesterol lipids from a low level. This rise is then maintained for over six hours, a much longer period of

time. It then returns to the low level during the fifteen hours of fasting. In this group the fat level stays high as the fat depots fail to deplete the high blood fat level.

The rise in cholesterol following fat ingestion as observed in this group of patients suggests that it is a utility substance and an intermediate stage of fat metabolism rather than a waste product.

CONCLUSIONS

1. There is no difference in fat digestion in the thin and obese individual.

2. The blood fat curve in the obese individual rises after fat ingestion, this rise being essentially cholesterol, and starts to fall after three hours. In the thin individual the rise in blood fat is in the non-cholesterol lipids. This rise is sustained for over six hours. These findings indicate that cholesterol is a utility substance and an intermediate stage of fat metabolism rather than a waste product.

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The Role of the Fat Soluble Vitamins A and D in Nutrition*

By

JACOB BUCKSTEIN, M.D.

NEW YORK, N. Y.

THE NATURE OF VITAMIN D

ALTHOUGH Tronseau (*Tronseau, A. Clin'cal Medicine, Philadelphia, 1882*) described the value of cod liver oil as a means of curing rickets, it was Hopkins (*Hopkins, F. G. The Analyst and The Medical Man. Analyst 31:385, 1906*) who suggested that an accessory food factor absent in the diet was the cause of the disease.

In this memorable article Hopkins wrote as follows:

"... no animal can live upon a mixture of pure protein, fat and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal body is adjusted to live either upon plant tissues or the tissues of other animals, and these contain countless substances other than the proteins, carbohydrates and fats.

"Physiological evolution, I believe, has made some of these well-nigh as essential as are the basal constituents of diet. Lecithin, for instance, has been repeatedly shown to have a marked influence upon nutrition, and this just happens to be something already familiar and a substance that happens to have been tried. The field is almost unexplored: only is it certain that there are many minor factors in all diets of which the body takes account.

"In diseases such as rickets, and particularly in scurvy, we have had for long years knowledge of a

dietetic factor, but though we know how to benefit these conditions empirically, the real errors in the diet are to this day quite obscure. They are however, certainly of the kind which comprises these minimal qualitative factors that I am considering.

"Scurvy and rickets are conditions so severe that they force themselves upon our attention, but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors."

This conception was further corroborated by the work of Funk in 1914 and Mellanby (*Mellanby, E. A Further Demonstration of the Part Played by Accessory Food Factors in the Aetiology of Rickets. (Proceedings of the Physiol. Society) J. Physiol. 52:LIII, 1918*) in 1918 who showed that when rickets was produced in puppies, the disorder could be prevented on a diet to which butter or cod liver oil had been added but could not be prevented by the addition of yeast, linseed, cotton seed or olive oil, or the proteins of milk or meat. Mellanby believed at the time that rickets was due to a deficiency of fat soluble vitamin A and that animal fats prevented the disorder. Mellanby employed the roentgen method as a means of demonstrating the presence of rickets.

The factor in food, the absence of which caused rickets, was found to be present in the unsaponifiable fraction of fish liver oils (*Zucker, T. F., Pappenheimer, A. M. and Barnett, M. Observations on Cod Liver Oil and Rickets. Proc. Soc. Exptl. Biol. Med. 19:176,*

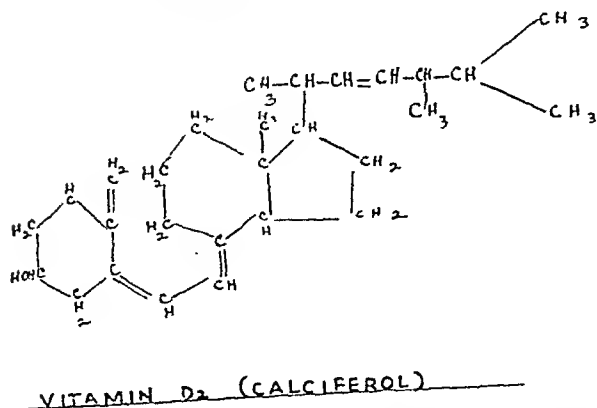
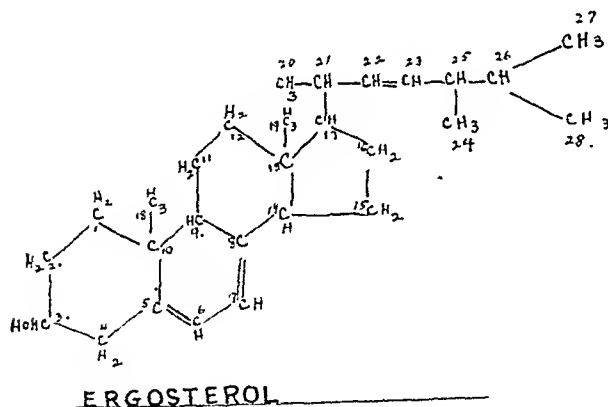
* Continued from July 1944 issue.
† Assistant Professor of Clinical Medicine, Cornell University Medical College.

1922). Zucker, Pappenheimer and Barnett employed the technique of Sherman and Pappenheimer of producing rickets in the rat on a phosphorus low diet. They then isolated the residue of unsaponifiable matter from cod liver oil. This material was then freed of most of the cholesterol. Fractions thus obtained when diluted with ninety parts of cotton seed oil (which itself was inactive) proved, to be even more curative than the original cod liver oil in the cure of the experimentally produced rickets. They suggested that although this curative fat soluble factor was not cholesterol, it was similar to cholesterol in its solubilities. They made the suggestion that this antirachitic factor might be a sterol related to cholesterol or a cholesterol derivative. The fatty acids of cod liver oil were found to be without effect in the cure of rickets. This antirachitic substance was finally named vitamin D by McCollum.

The Chemical Structure of Vitamin D

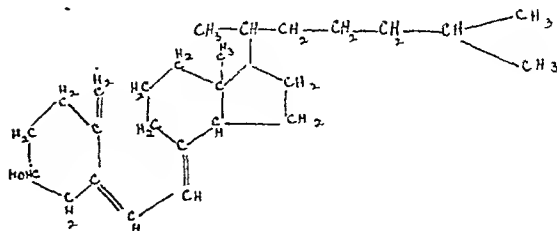
Ergosterol, a sterol compound, was first isolated from ergot by Tanret. This provitamin, ergosterol, is synthesized by yeast and other organisms. It has a characteristic absorption spectrum in the ultraviolet region. It is activated to vitamin D by ultraviolet light.

It has also been shown that there are at least ten substances known as sterols which are capable of being activated into rickets curing compounds. The chemical relationship of ergosterol to vitamin D is shown by the following formulae:



The type of vitamin D however, present in fish liver oil was found to be different in the main from that de-

rived from ergosterol as shown in the formula below (Waddell, J. Provitamin D of Cholesterol. J. Biol. Chem., 105:711, 1934).



VITAMIN D₃ (ISOLATED FROM FISH LIVER OIL
AND ALSO PREPARED BY IRRADIATION
OF 7-DEHYDROCHOLESTEROL)

Waddell found in his experiments that ten rat units per hundred gm. of fish liver oil afforded ample protection against the development of leg weakness in baby chicks. On the other hand twenty five or more times that number of rat units if irradiated ergosterol were essential to afford a similar degree of protection. It was this type of experimental evidence that led him to the conclusion that vitamin D of fish liver oils differed from that obtained by the irradiation of ergosterol.

This conclusion as to a difference in the nature of the two vitamins D confirmed the observations of other investigators such as Russell and those of Steenbock.

The type of vitamin D in the fish liver oil was discovered to be that derived from activation of 7-dehydro-cholesterol. This is the form most commonly found not only in fish liver oils but also in the skin of the human being and is described as vitamin D₃ in contradistinction to the calciferol derived from ergosterol and known as vitamin D₂. The latter type is found in yeast and ergot. The irradiated ergosterol is also known commercially as "viosterol."

What was originally considered as vitamin D₁ was shown to be a mixture of calciferol and lumisterol, the latter product also resulting from the irradiation of the provitamin ergosterol. It is therefore no longer considered as a separate form of vitamin D.

At least eight other vitamins D in addition to the accepted D₂ and D₃ are believed to exist (Bills, C. E. The Chemistry of Vitamin D. J. A. M. A. 110:2150, 1938).

Although activated 7-dehydro-cholesterol has been prepared in crystalline form, it has not been possible to do so from the natural sources in fish liver oils such as that obtained from the halibut.

Vitamin D was isolated from fish liver oils in the form of crystallized esters however, by Simons and Zucker (Simons, E. J. H. and Zucker, T. F. Antirachitic Substance of Tuna-Liver Oil. J. Am. Chem. Soc. 58:2655, 1936) and Haslewood and Drummond (Haslewood, G. A. D. and Drummond, J. C. Antirachitic Substance from Tunny Liver Oil. Chem. and Ind. 55:508, 1936).

The first crystalline preparation of vitamin D from activated ergosterol was obtained by Reerink and van Wijk (*Reerink, E. H. and van Wijk, A. The Photochemical Reactions of Ergosterol. Biochem. 23:1294, 1929*): When fed to children and rats having rickets, this crystalline substance obtained by long-wave irradiation of ergosterol, proved to be powerful in its anti-rachitic potency and apparently identical with vitamin D. The pure compound was isolated by Linsert and Windaus.

The determination of the presence of vitamin D depends primarily on biological procedures. The test animals are usually rats and chicks, the rat being the animal ordinarily employed. The rat is placed on a diet capable of producing rickets. It is then fed on varying amounts of the vitamin D substance undergoing test. This is carried out for a period of six to ten days when the animal is killed. Several methods are then employed for determining the effectiveness of the vitamin D in producing bone changes. The "line test" originally described by McCollum, Simmonds, Shipley and Park (*McCollum, E. V., Simmonds, N., Shipley, P. G. and Park, E. A. Studies on Experimental Rickets (A Delicate Biological Test for Calcium-depositing Substances. J. Biol. Chem. 51:41, 1922)* depends on the demonstration in the proximal end of the tibia of a new line of calcification in the rachitic bone which has been removed from the animal and treated chemically. Its value has been verified by Bills (*Bills, E. A. Critique of the Line Test for Vitamin D. J. Biol. Chem. 90:619, 1931*).

Longitudinally sectioned halves of the proximal end of the tibia are placed in a one percent solution of silver nitrate and exposed to sunlight or to the light of a Mazda lamp and studied by means of a low power binocular microscope. Silver phosphate is formed which is reduced to black silver, thus producing a line at the zone of calcification. This line occurs in the proliferative zone of the cartilage and may be uninterrupted or fragmentary depending on the amount of calcium deposited. Another method is that of determining the healing of bone by radiographic examination.

The International standard of vitamin D as adopted by the Health Organization of the League of Nations is determined as follows: Irradiated ergosterol specially prepared is dissolved in olive oil. One unit is the equivalent of "the vitamin D activity of 1 milligram of the International standard solution of irradiated ergosterol," which has been found equal to that of 0.023 microgram of crystalline vitamin D." (*Report of the Conference on Vitamin Standards, Geneva Publications Department of the League of Nations, No. C. H. 1055 (1), 1931*). A U.S.P. unit of vitamin D is the equivalent in anti-rachitic potency of the International Unit of vitamin D.

The International Unit when given over a period of eight days to a rachitic rat causes a deposition of sufficient calcium in the cartilage to produce the "line." It is against this power of the International Unit that the tested substance is compared.

It is significant that it is vitamin D₂ that is identical with that in milk and eggs and particularly with the natural vitamin D of fish liver oils. Also vitamin D₂ is

the form of the vitamin that is absorbed into the blood stream after ultraviolet irradiation of the skin or exposure to sunlight. The natural vitamin D₂ is probably superior to the artificially prepared vitamin D₃ also known as calciferol or viosterol for two main reasons. In the first place the artificial product may not be entirely free of by-products, the effect of which may be undesirable. In the second place, the natural sources also contain vitamin A. There is still a third reason for the superiority of the natural sources of vitamin D and this is based on actual experimental evidence on the rat, an excellent laboratory animal for testing the anti-rachitic value of a substance. Indeed the unit of the U. S. Pharmacopeia and the International Unit is based on the curative effect on the rat. If a rat unit of the natural vitamin D is fed to the chick its potency is considerably greater than if a rat unit of the artificially prepared vitamin D is substituted in its place. Fish liver oils are therefore among the particularly valuable sources not only because they contain vitamin D in natural form but also because they possess the combination of both the fat soluble vitamins A and D.

SOURCES OF VITAMIN D

The importance of available sources of vitamin D is indicated by the following facts.

It is interesting to note that the foods which make up the average diet are markedly deficient in vitamin D. Thus muscle meat, the glandular organs, the fruits, vegetables, cereals and sugar contain practically no vitamin D. The amount present in milk and butter is very small.

The vitamin D content of milk shows considerable variation depending on the season of the year. Thus in the milk obtained during the summer, the vitamin D content is equal to forty units to each quart. During the winter, the vitamin D content of the milk is equivalent to five units, an essentially negligible amount. (*Bechtel, H. E. and Hoppert, C. A.: Study of Seasonal Variation of Vitamin D in Normal Cow's Milk. J. Nutrition 11:537, June, 1936*).

Bechtel and Hoppert made a monthly assay of milk fats from a number of sources for the vitamin D value. They found that milk might show as great a variation as 900 percent in anti-rachitic potency. The richness of vitamin D content was greatest during July, August and September. The lowest values occurred in February. The milk of Guernsey cows showed variations in vitamin D potency from 4.8 to 43.8 U.S.P. units per quart. The milk of Holstein cows showed variations in vitamin D value ranging between 3.1 to 27.7 U.S.P. units per quart. Exposure of the cows to sunlight during the summer months appeared to be the essential factor responsible for the increased vitamin D potency of milk during the summer season.

The same seasonal variation is to be found in the case of eggs. When eggs obtained in February are examined for their vitamin D content, the amount present is the equivalent of 140 units per hundred grams, this being entirely present in the yolk of the egg. During the summer, the vitamin D content rises to 390 units per hundred grams (*de Vaucy, G. M.,*

Munsell, H. E., and Titus, H. W.: *Effect of Sources of Vitamin D on Storage of the Antirachitic Factor in the Egg*, *Poultry Sc.* 12:215, 1933).

The egg yolks of at least five eggs may be necessary to furnish the amount of vitamin D obtained from a single teaspoonful of cod liver oil. Since one teaspoonful of halibut liver oil contains four times as much vitamin D as one teaspoonful of cod liver oil, it would thus mean that one fourth teaspoon of halibut liver oil would contain as much vitamin D as a minimum of five egg yolks. Since halibut liver oil is also much richer than cod liver oil in vitamin A, the halibut liver oil would have this further advantage.

Milk and eggs therefore contain at best comparatively small amounts of vitamin D and even this is of an extremely variable character, being particularly small in amount during the winter.

The liver of mammals also contains comparatively small amounts of vitamin D and may be extremely variable in its content (*de Fancey, G. M. and Munsell, H. E.: Vitamin D Content of Calf, Beef, Lamb and Hog Liver. J. Home Econ., 27:240, 1935*).

In the fish liver oils we have a superior source of vitamin D. By a process of concentration of fish liver oils comparatively small amounts may be administered containing large quantities of vitamin D.

An important source of vitamin D is that obtained from the activation of 7-dehydro-cholesterol in the skin through irradiation by the short ultraviolet rays of the sun. Here too there is marked seasonal variation since there may be little exposure to the rays of the sun during the winter period of the year.

The relation of exposure to sunlight to the activation of the provitamin in the skin, with the formation of vitamin D, has been demonstrated by a number of observers.

Palm in 1890 (*Palm, T. A. The Geographical Distribution and Aetiology of Rickets. Practitioner 45: 271, 321, 1890*) described the curative value of sunlight in rickets. He showed that the distribution of the disease varied with the availability of sufficient sunlight and that in those areas in which rickets was commonly present a deficiency of sunlight appeared to be the most important element in the etiology of the disease. He quoted a missionary in China, Dr. Dugald Christie, who stated that in spite of the absence of any sanitary measures, he had failed to find a single case of rickets during a period of six years while living in Manchuria. This was similarly true of other regions of China, India and Japan. Their immunity to the development of the disease appeared to be associated with the fact that the inhabitants were subjected to abundant sunlight. On the basis of these findings he recommended the use of sun baths both for the prevention as well as the treatment of rickets.

It was Huldschinsky who in 1919 showed the curative value in rickets of artificial light emanating from a quartz lamp. He controlled his studies by x-rays which

demonstrated the ultimate cure of the disease by the restitution of the bone to normal.

Hess and Unger (*Hess, A. F. and Unger L. J. The Cure of Infantile Rickets by Artificial Light and by Sunlight. Proc. Soc. Exptl. Biol. Med., 18:298, 1921*) also showed the curative value of sunlight in rickets and that the disease could be prevented under the influence of light even when the animal was subjected to a deficient diet, ordinarily capable of producing the disease. They employed the mercury-vapor lamp with exposures made every few days lasting from three to twenty minutes at a distance varying between 120 to 75 cm. The cure of the disorder was indicated not only by the evidence on clinical examination but also by the roentgen evidence of calcification at the ends of the bones. Similar evidence was also observed from the exposure to the sun's rays in increasing degree, of infants suffering from rickets. The diet in both cases was not altered. They demonstrated the value of sunlight both natural and artificial, in the prevention and cure of infantile rickets.

Origin of Vitamin D in Fish Liver Oil

The origin of the large amounts of vitamin D in fish is a problem of considerable interest. It is believed that one source is in the vitamin D present in some marine micro-organisms (*Darby, H. H. and Clarke, H. T. The Plant Origin of A Vitamin D. Science 85: 318, 1937*). By means of spectrographic studies Darby showed the presence of ultraviolet light, in the first three feet of water below the sea. Examination of the Sargassum weed, an alga, which grows at shallow depths in the waters of the Caribbean showed the presence of a lipid fraction which possesses antirachitic therapeutic potency. The action of the ultraviolet light penetrating through the water, produces vitamin D in the algae. Much of this weed eventually finds its way into the Gulf Stream and further northward. During its passage it becomes infested with various invertebrates that apparently obtain part of their nourishment in this manner. Thus the vitamin D of the algae may be transferred to the invertebrate animals which in turn become food for the larger fish. The common association of both vitamin A and D in fish liver oils may also be intelligently explained on the basis of such a transition.

Apparently the vitamin D in the micro-organisms is altered somewhat in chemical structure within the fish itself. The reason for this assumption is that when the vitamin D obtained from these micro-organisms is fed to chickens, it is relatively inactive. The vitamin D from fish oil, however, is biologically highly active. If the origin of vitamin D in the fish liver is therefore to be traced to these micro-organisms as a primary source, some chemical transformation obviously takes place within the fish itself. The ability of man to utilize the vitamin D obtained from fish liver oils is unquestioned.

(To be continued in September issue)

Book Reviews

Elimination Diets and The Patient's Allergies. A Handbook of Allergy. By Albert H. Rowe. 2nd Edition, pp. 256 (\$3.50). Philadelphia, Lea and Febiger, 1944.

The importance of food allergy in the production of many allergic manifestations including asthma, rhinopathy, urticaria, angioneurotic edema, neurodermatitis, infantile eczema, migraine, some gastro-intestinal and hepatic syndromes and even certain cardio-vascular manifestations becomes more and more apparent as our knowledge broadens and deepens. However, it is necessary that the physician learns that skin tests frequently are not infallible, probably because very often not the skin but other organs are the allergic shock structures. It was Rowe who 18 years ago introduced the elimination diets in order to ascertain whether a given food is the responsible cause for an allergic manifestation. This pioneer has now the great satisfaction that the principle of his oral food tests is accepted by many accredited men in medicine.

In a very comprehensive and lucid fashion Rowe summarizes in the present volume his work with food trial tests and gives his new revised diets together with most minute suggestions for menus and recipes so that every patient can follow the orders without difficulties and without danger of nutritional impairment. In addition to his four basic elimination diets, Rowe gives detailed directions for cereal-, egg-, milk-, and fruit-free diets and diets for diabetics or other patients who need a reducing regimen.

While food allergy in all of its clinical manifestations is discussed in some detail, the handbook gives also a valuable synopsis of diseases caused by inhalant allergens, contactants, injectants and infectants. In addition, there is a very useful discussion on many of the more important allergens as to where they occur and where they should be suspected.

The usefulness of the volume is enhanced by an appendix on the daily nutritional requirements including vitamins, a detailed questionnaire for the allergic patient, a food diary, instructions for the establishment of environmental control, and a standard list of contactants. This handbook can be recommended unreservedly to every one who has to deal in his practice with allergy, practitioner and specialist alike.

An Outline of General Physiology. By L. V. Heilbrunn. 2nd Edition, 748 pp., (\$6.00). Philadelphia, W. B. Saunders Co., 1943.

General physiology is a term which has meant different things to different men. Professor Heilbrunn rightly considers general physiology as a science in its own right and not merely a diluted mammalian physiology. The nature and mechanisms of living matter are the boundaries of its scope, presenting a field for study which is limitless. The activities of the cell, if understood, should one day reveal much about the activities of the organism. The general physiologist studies the individual units of the complex system that make up the organism whilst the mammalian physiologist studies the activities of the organism as a whole.

The first edition of this volume found a receptive audience badly in need of what Professor Heilbrunn presented. The present edition will undoubtedly be well received. The book is for the graduate student and other serious workers in physiology, but will be of interest to less advanced students as well. It is hoped that a course such as is here outlined will some day be a prerequisite to the study of medicine. Until then, the student can do no better than become acquainted with the book. The bibliography is fairly thorough, and will be of great aid to the investigator wishing to trace original work.

Abstracts of Current Literature

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

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*J. EDWARD BERK
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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

TURNER, G. G.: *Fibrous stricture of gullet after nineteen years' duration.* (Brit. J. Surg., V. 30, P. 344, Apr. 1943.)

Post-inflammatory strictures of the esophagus, as the result of swallowing chemicals, may be particularly

difficult to manage. The present case of a 26 year old doctor with a fibrous stricture at the esophagus at the level of the seventh dorsal vertebra, of 19 years' standing, was unsuccessfully treated for 2 years by numerous attempts at anterior dermato-esophagoplasty. This left the patient with cervical esophageal and gastric fistulae which he connected with rubber tubing and

lived thus for 13 years, until gastric distress brought him to the hospital.

Successful and satisfactory dilatation of the stricture was obtained by systematic bouginage so that in 2 months solid and semisolid food was passed. This case lends strength to the author's belief that in most fibrous strictures of tubes a small residual mucous-lined passage remains, which may then be dilated by the intelligent use of bougies. He recommends, on this basis, the method of swallowing bougies, instead of "passing" them, a method he previously proposed in 1939.—J. Garcia-Oller.

STOMACH

AVERS, M. A.: *A study of hematopoiesis in a group of female students ages fifteen to twenty-three years through a study of gastric secretion and correlated blood counts.* (*Amer. J. Med. Tech.*, V. 10, P. 1, Jan. 1944.)

The acid values for the gastric contents following a Ewald test meal were found to be dependent on a variety of factors which may make the results undependable. Among these factors were dilution, buffering and neutralization by the meal, speed of gastric evacuation, rate of gastric secretion, psychogenic factors, and functional states of organs other than the stomach. More rigid control procedures for obtaining gastric contents are recommended. The hemoglobin content was found to have a definite, though not significant, relationship to the acidity of the gastric contents, alterations in both occurring in the same direction.—I. M. Theone.

FARRIS, J. M., RANSOM, H. K. AND COLLIER, F. A.: *Total gastrectomy; effects upon nutrition and hematopoiesis.* (*Surgery*, V. 13, P. 832, 1943.)

Following total gastrectomy in the human there is not the disturbance in protein digestion which one might suppose would occur due to absence of pepsin digestion nor is there pernicious anemia due to absence of the intrinsic factor. Anemia due to lack of iron absorption may occur, however. This is the result of inability of the intestinal tract to convert the inabsorbable iron to the ferrous state. Hydrochloric acid given with the diet may connect this. The hypochromic microcytic anemia may also be avoided by administering ferrous sulfate, 0.32 gm three times per day for seven days each month.—I. M. Theone.

MARXER, O. A.: *Polyps of the stomach and polypoid gastritis.* (*Quart. Jour. Med.*, V. 12, P. 1, 1943.)

The clinical features of gastric polyps and polypoid gastritis are discussed and the radiology, gastroscopic appearances, pathology, and history of both are illustrated by radiographs, drawings and photographs. Clinical and pathological material is tabulated in appendices. Gastric polyp is usually papilloma or adenoma, or leiomyoma. In the course of X-ray examination of 4424 consecutive patients, 10 polyps were diagnosed. From colleagues and the literature, an additional 89 cases were collected and symptoms reviewed, while 24 museum specimens without histories were

tabulated. Variable dyspepsia and hemorrhage are the usual symptoms. Malignancy occurs in about 20 per cent. Diagnosis is by radiology or gastroscopy. Similar symptoms occur with polyps of varying pathologic nature. Polypoid hyperplastic swellings occurred in 19 patients complaining of dyspepsia with inconstant food relations. Free hydrochloric acid was usually present in those with ulceration. In those with low acid there was much degeneration of gastric epithelium. In nearly all without ulceration free hydrochloric acid was absent or low. The patients were all observed or reported upon at intervals for several years.—Courtesy Biological Abstracts.

BOWEL

CURTIN, V. T.: *Use of blood plasma intraperitoneally in treatment of gastroenteritis in infants.* (*Penn. Med. J.*, V. 47, P. 575, March 1944.)

Frozen plasma which had been thawed was administered by syringe into the peritoneal cavity of the infant. This simplified the problem of transfusions when veins were difficult to enter and probably the procedure could be used in the adult as well. About 60 cases of acute gastroenteritis were treated, each infant receiving from 75 to 100 cc plasma. Only occasionally was more than a second transfusion needed. The improvement in the condition of the patient was prompt and permitted the physician more time to determine carefully the proper diet required. Other conditions besides gastroenteritis were similarly treated, including hemorrhagic disease of the new-born and post-operative distress in pyloric stenosis. The results were very encouraging.—G. Klenner.

CHRISTOPHER, F.: *Subparietal rupture of the intestine due to unmuscular effort.* (*Surgery*, V. 15, P. 628, April, 1944.)

Subparietal rupture of the intestine due to muscular violence is extremely rare. A total of about 49 cases have been reported in the literature. The present case is the 50th. All the patients were men. Hernia was present in 37 cases and definitely stated to be absent in only 4. The mortality was 56 per cent.

The most likely explanation appears to be that increased intraluminal pressure in the intestine resulting from the muscular exertion produces a rupture at some weak point.

Operation in the present case was performed about five hours after the rupture occurred and was successful. Literature reports show the mortality to be more than 50 per cent if operation is performed after twenty-four hours have elapsed.—D. A. Wocker.

SHIRELY, F. T., AND RENSCHAW, R. J. F.: *Mesenteric thrombosis.* (*Cleveland Clinic Quart.*, V. 10, P. 133, Oct., 1943.)

This report is of an atypical case of mesenteric thrombosis in which the course was slow and progressive. In the usual case there is an acute condition of the abdomen developed with rather sudden onset. Colicky pain is the outstanding symptom. In the present case the patient noted colicky pain in the abdomen es-

pecially after meals. Frothy vomiting occurred with the pain but these symptoms lasted only a short while following which the patient was free from distress for thirteen months.

The pain recurred and increased in severity for approximately a two week period when the patient came to the hospital. Examination showed no acute abdominal symptoms. The pulse, temperature and blood pressure were normal. However a gastro-intestinal roentgenologic examination indicated a gastric ulcer and therefore the condition was treated as such.

The abdominal pain became worse gradually, until sixteen days later the condition was acute. The abdomen was tender, rigid but not boardlike. The leukocyte count was 16,000. The condition was diagnosed as intestinal obstruction with probable sigmoidal diverticulitis. Jaundice appeared and deepened but this was attributed to the sulfa therapy being used. After two weeks of treatment an exploratory operation of the right upper quadrant was performed and revealed hepatitis of the liver, a normal stomach and normal biliary tract. The patient died in the next twenty-four hours. The autopsy showed the entire small and large bowel to be gangrenous, and the mesenteric arteries and the splenic artery to be completely occluded by a severe degree of arteriosclerosis.

In retrospect the initial attack was considered due to a small infarction, which was followed 13 months later by gangrene and sloughing of the bowel due to the gradual progress of the arteriosclerotic condition finally depriving the bowel of an adequate blood supply.—C. G. Clements.

D'ONOVIO, F. R., J. BELLINGI, AND H. MATURI: *Asthenic peritonitis due to perforation of tuberculous intestine.* (*Rev. Med. Rosario*, V. 33, P. 801, 1943.)

Perforation of intestinal tuberculous ulcers is rare despite the high incidence of intestinal tuberculosis. Clinical study of 6 cases, with necropsy findings in 5, is reported. The resultant peritonitis was of the asthenic type.—Courtesy Biological Abstracts.

MEYER, A. W.: *Lymphocytic hyperplasia and "spontaneous" alimentary lesions.* (*Calif. and West. Med.*, V. 59, P. 210, 1943.)

In studying the striking transitions in the squamous epithelium under the surface of faucial and pharyngeal tonsils and in their crypts, the author found that similar infiltration and destruction of the epithelium occurred wherever hyperplastic lymph nodules, isolated or aggregate, were present. This phenomenon was especially common and probably universal in appendices not known to be or regarded as diseased. The reaction of the lymphatic nodes to physiological states such as exercise, pregnancy, etc., also is well established and they may be allergic to various inhaled as well as ingested substances. Such allergic reactions might explain recurrent light or severe attacks not only of tonsillitis and appendicitis but of ulcer—especially esophageal, gastric, or duodenal ulcer. The destruction of the appendicular epithelium and mucosa, in consequence of non-infectious processes, offers a satisfactory explanation for the

normal, non-pathologic obliteration of the appendix; this is effected from below and not from the surface. Thus the control of lymphatic hyperplasia may point the way to relief from various lesions of the alimentary tract.—Biological Abstracts.

MAMMANA, C. Z.: *Intestinal invagination, I.* (*Anais Paulistas Med. e Cir.*, V. 46, P. 5, 1943.)

The first portion of a general discussion of the important problem of intestinal invaginations, particularly in young children. Emphasis is placed on methods of early diagnosis and on means of surgical treatment of the condition.—Biological Abstracts.

MAMMANA, C. Z.: *Intestinal invagination, II.* (*Anais Paulistas Med. e Cir.*, V. 46, P. 83, 1943.)

The conclusion of a general discussion on intestinal invaginations, with special emphasis on methods of diagnosis and on treatments. Surgical methods are described in detail.—Biological Abstracts.

PANCREAS

BAUMAN, L. AND WHIPPLE, A. O.: *Diagnostic value of pancreatic function tests in 47 surgically treated cases.* (*Am. J. Med. Sci.*, V. 207, P. 281, March, 1944.)

By the use of a bilumen tube, the gastric contents were prevented from entering the intestine during the period of aspiration of the pancreatic juice from the duodenal lumen. This precaution was necessary to prevent destruction of the pancreatic enzymes by the acid. Secretion was induced by injection of mecholyl.

Disturbances in the secretion of the pancreatic acini were noted even in cases where no histologic evidences of pancreatic damage were found. A normal range of pancreatic enzyme concentrations in cases with painless obstructive jaundice was believed indicative of carcinoma of the duct. On the other hand, painless obstructive jaundice with a low range of concentration of enzyme was believed to be indicative of carcinoma of the pancreas. Tumors of the ampulla of Vater were associated with normal enzyme values if there was an accessory pancreatic duct or if the main pancreatic duct entered separately from the common bile duct.—G. Klenner.

FELSEN, J., WALARSKY, W., AND ROSEN, E.: *Cystic fibrosis of the pancreas in siblings, with necropsy reports.* (*Arch. Pediat.*, V. 60, P. 488, Sept. 1943.)

Cystic fibrosis of the pancreas appears as the cause of death in about 3 to 4 per cent of the necropsy reports of infants. Two cases are reported here which were siblings, and hence pointing toward a congenital factor as being the cause instead of inflammation or vitamin A deficiency.

A male baby weighing 6 lbs. 6 ounces at birth appeared normal and passed meconium for two days, and then nothing for the following three days. On the sixth day food was regurgitated with each feeding; the abdomen became distended; an enema of bicarbonate of soda produced only a small amount of green stool; a barium enema released a mucous cast by rectum and a Levine tube brought up 60 cc of yellowish fluid. The

baby died. Necropsy findings showed a perforation at the mid-transverse colon with passage of about 300 cc of foul-smelling fecal-like fluid into the peritoneal cavity. The visceral organs were normal grossly. On section the pancreas showed marked cystic dilatation of the ducts, the lumen being filled with either granular material or large pale cells. The pancreatic duct however was not closed. The secretory portion of the gland was largely replaced by fibrous tissue though the islets were intact.

A female baby was born to the same mother a year later. This baby had no bowel movements from its day of birth. Its abdomen became distended, and vomiting occurred. The baby was operated on for volvulus but none was found. On the 20th day bronchopneumonia developed and the baby died on the 27th day of life. Necropsy findings showed no gross pathology of the visceral organs. On section the following were noted: The pancreas showed cystic changes of the ducts which were filled with hyaline material, no obstruction of the pancreatic duct, and interstitial fibrosis of the glandular elements of the pancreas.—C. G. Clements.

PIRINI, ALFREDO AND ALFREDO GUILLANO: *Pancreatoccholeperitonium or bilio-pancreatic peritonitis. Comment on 3 observations.* (Rev. Asoc. Med. Argentina, V. 57, P. 97, 1943.)

Acute pancreatitis and cholecystitis with leakage may coexist. Biliopancreatic peritonitis is in general treated as acute pancreatic necrosis; various surgical procedures and the prognosis are discussed.—Courtesy Biological Abstracts.

ULCER

LANE, R. A. G.: *The peptic ulcer problem. A series of 181 cases from the Royal Canadian Navy.* (Canadian Med. Assoc. J., V. 50, p. 353, April, 1944.)

A major medical problem of the war is dyspepsia and recognition of this fact led to establishment of a special gastro-intestinal clinic. The cases presented are from this clinic, being admissions from January, 1942 to July, 1943. Fifty-five per cent of the 181 cases of peptic ulcer were retained in the Service but assigned to protected jobs and areas on shore. In 45 per cent of the cases the onset of symptoms antedated enlistment. Sixteen of the ulcer cases (8.8 per cent) were gastric, the remaining 165 cases were duodenal. Hemorrhage occurred in 8.2 per cent, perforation in 4.9 per cent and obstruction in 1.1 per cent. Occult blood in stool was found in 45 per cent. Four cases had sub-total gastrectomy performed; all are still in the Service and are considered in a safer condition than before operation.—F. E. St. George.

SURGERY

LAHEY, FRANK: *A simple useful anterior gastroenterostomy.* (Surg. Gyn. and Obstet., V. 78, P. 169, Feb., 1944)

For gastric ulcers located low in the stomach or fused with the bile tract, and where subtotal gastrectomy is unduly hazardous, Dr. Lahey recommends

a simple anterior gastroenterostomy. He uses this operation in preference to the popular "no loop posterior gastroenterostomy" which has many undesirable features such as the difficulty of operating for recurrent stomal ulcers or doing a subsequent subtotal gastrectomy.

The anterior gastro-enterostomy advised consists of removing the omentum well over to the left side of the stomach, thus freeing the greater curvature. This margin can then be held up by a Babcock clamp and the jejunum attached to the stomach just posterior to the greater curvature. The afferent and efferent loops of the jejunum are not anastomosed. The advantages of this operation are that while performing it the stomach is easily visible, the anastomosis can be done without clamps or tension, the size of the stoma is not limited, and the gastric contents gravitate away from the site during the procedure. No jejunojejunostomy between the efferent and afferent loops was done as Dr. Lahey believes the alkaline jejunal content of the proximal loop should be allowed to press into the stump of the resected stomach to neutralize and lower the gastric acidity in the remaining gastric stump.—C. G. Clements.

CONNER, G. J. AND HARVEY, S.: *Colostomy of the ascending colon or cecum.* (Yale J. Biol. Med., V. 16, P. 261, January, 1944.)

The operation called cecostomy should establish a vent from the right colon to the outside. This should be done safely and directly with as little visceral manipulation as possible and by avoiding sutural perforations of the gut, thus preventing the formation of an avenue for the escape of liquid feces into the abdominal cavity.

Use of a simple procedure is recommended. Fine silk interrupted sutures should be used throughout.

Careful attention will protect the function of the colostomy. When its usefulness is passed the mucosa is trimmed down about a centimeter below the skin edge and the wound will close. No anesthesia is found necessary. Surgical decompression of the ascending colon is achieved with the advantages of controlling infection and reducing the likelihood of post-operative hernia.—John Cox.

EXPERIMENTAL MEDICINE

SECRETION

JALRYI, OSMO: *The restitution of secretory material in the great sublingual gland of the cat as studied by the fractional analysis method. II. The rhythmic work of the cells and the gland.* Zeitschr. Zellforsch. u. Mikrosk. Anat. Abt. A: (Allg. Zellforsch. u. Mikrosk. Anat.), V. 30, P. 156, 1940.)

The cells were counted at intervals after an injection of pilocarpin. Maximum of extrusion in albuminous cells was found from 15 minutes to two and a half hours with 92 per cent of the cells in this phase between one half and one hour. The first replacement had its maximum (70-30 per cent) between one and three and a half hours and after eleven hours fell below 10 per cent. A 3rd maximum of the

2nd replacement occurred after 5 to 7 hours and continued at a level of 67 and 90 per cent. After 7 hours storage began but did not exceed 26 per cent. In starvation the 2nd replacement phase prevailed over storage by an average of 94 per cent. The high percentage of cells in the same phase indicates synchronous activity. The findings after pilocarpin were not duplicated after ordinary meals. Thus, an ordinary stimulus allows the cells to continuously replace expelled granules or, in other words, to work continuously. Only the stronger stimulus produces "pseudo-rhythmic" activity. The cells of the same acinus are more accurately synchronized than those of different units. Since pilocarpin had a similar effect on both kinds of cells, parasympathetic innervation is suggested by these observations.—Courtesy Biological Abstracts.

ABSORPTION

INGELTINGER, A. F., MOSS, R. E. AND HELM, J. D.: *The effect of atropine upon the absorption of vitamin A.* (*J. Clin. Invest.*, V. 22, P. 699, Sept., 1943.)

In patients with sprue the record of the motility of the small intestine shows a pattern similar to that of the normal person's intestine following the administration of atropine. It has been suggested that in sprue absorption from the intestine is decreased because of the decreased motor activity. This led to the interesting concept that following atropine intestinal absorption in the normal individual would be depressed since it is also in patients with sprue.

Twenty-three studies on vitamin A absorption were carried out in six individuals who showed no signs or symptoms of gastro-intestinal disease. Following atropine sulfate injection, the appearance of vitamin A in the blood (plasma) was greatly delayed when the vitamin A was introduced into the small intestine. While the decreased intestinal motility attending atropinization may have been responsible for the decreased absorption, the authors found no direct evidence to support this. Some of the reduction in absorption may have been produced by the inhibition of the pancreatic and biliary secretion following atropinization but the mechanism of this reduction is obscure.—M. H. F. Friedman.

EXCRETION

SHAY, H., KOMAROV, S. A., SIPLET, H. AND FELS, S. S.: *Excretion of certain of the newer sulfonamides in the bile and urine.* (*Am. J. Med. Sci.*, V. 207, P. 550, April, 1944.)

Acute experiments on thirty specially prepared dogs were performed. These dogs were so prepared that the hepatic and gallbladder bile could be collected simultaneously after the instillation of 0.2 gm/kilo of the various drugs in saline through a duodenal cannula. The drugs studied were phthalyl sulfathiazole ("sulfathalidine") succinylsulfathiazole ("sulfasuxidine") sulfamylguanidine ("sulfaguanidine") and sulfathiazole. Bile and urine samples were collected continuously for 8 to 10 hours, fractionated at two hour intervals, with peripheral blood samples taken at these times.

The blood levels reached for "sulfasuxidine" and "sulfathalidine" were very low as compared with sulfathiazole and "sulfaguanidine". The hepatic bile/blood concentration ratio was found to be considerably increased for "sulfasuxidine" over that for sulfathiazole and many more times for "sulfathalidine," while "sulfaguanidine" was excreted by the liver at approximately the same concentration as in the blood. It seemed that the introduction of the phthalyl or succinyl radicles into the sulfathiazole molecule at the N⁴ position resulted in a greater selectivity by the liver in the removal of those drugs from the blood with preference for the phthalyl radicle. "Sulfathalidine" also seemed to be partially broken down in the dog's liver with the liberation of a free sulfonamide, presumably sulfathiazole.

The gallbladder concentrated all the drugs with the exception of "sulfaguanidine" in proportion to the water absorbed from the bile. It neither absorbed or excreted any of the drugs, but was able to absorb "sulfaguanidine." Sulfathiazole and "sulfaguanidine" appeared to be excreted in the urine by the glomerular filtration mechanism, while "sulfasuxidine" and "sulfathalidine" are suspected of being secreted by both the tubules and the glomeruli.—H. Siple.

PATHOLOGY

MORRISON, T. G.: *Effects of estrogens on the testis in hepatic insufficiency.* (*Arch. Path.*, V. 37, P. 39, Jan., 1944.)

After a very brief review on the past research done on the subject by other workers, the author presents his work. The aim was to investigate the state of the human testes in various conditions of hepatic insufficiency and to test the validity of the hypothesis that excess of estrogenic substances is active in the production of testicular changes. Hepatic failure, excess estrogens and alcoholism were considered as possible factors operating to produce these changes.

The author studied 28 human cases of Laennec's cirrhosis. Of these 16 instances (57.1 per cent revealed the presence of significant testicular atrophy. The incidence was 90 per cent in persons below 50 years of age and 38.9 per cent in persons above 50. From the author's study no evidence was found which would indicate a direct causal relation between alcoholism and atrophy of the testes unless the alcoholism was concurrent with severe hepatic damage. In cases of hepatic failure other than Laennec cirrhosis, in order for atrophy of the testes to result, there must be damage severe, extensive and of long standing. Finally the author presents animal experiments the results of which point to failure of hepatic inactivation rather than to failure of biliary excretion of estrogens as the mechanism by which testicular atrophy occurs.—C. Foderaro.

POPPER, H., GYONGY, P. AND GOLDBLATT, H. *Fluorescent material (ceroid) in experimental nutritional cirrhosis.* (*Arch. Path.*, V. 37, P. 161, March, 1944.)

The authors present a discussion of a golden brown fluorescent material which they studied in livers of

rats with experimental cirrhosis. They describe its appearance under the fluorescence microscope as well as other properties. The material is apparently identical with ceroid. Its presence is not related to hepatic necrosis with or without hemorrhage, nor with destruction of large quantities of blood. Its presence is often associated with cirrhosis, but the two need not necessarily be combined. Cystine enhances its deposition; choline alone, choline with cystine, and para-methylaminobenzene, prevent its deposition. It is believed to develop from cells containing fat and to be related to the fatty stages in the development of cirrhosis.—C. Foderaro

DENN, J. S., KIRKPATRICK, J., MELTCHER, N. G. AND TILDER, S. V.: *Necrosis of the islets of Langerhans produced experimentally.* (*J. Path. Bact.*, V. 55, P. 245, July, 1943.)

The finding in human pathology of necrosed Langerhans cells, tho rare, is not altogether unknown. Cases have been reported, one in a severe diabetic child, two of hyperthyroidism with glycosuria, and one in a non-diabetic with lobar pneumonia. The experimental production of selective necrosis of the islets with ensuing diabetes by the intravenous injection of alloxan in rabbits, mice, and rats suggests a mechanism for the "initial disturbance of the islet system which may eventuate in diabetes mellitus." The injection is followed by an initial hyperglycemia and a subsequent hypoglycemia which may be fatal. Body temperature is very low.

The mechanism of production is discussed with special reference to the view that "it is determined by excessive stimulation and functional over-activity of the insular tissue." The method is presented as a contribution to the armamentarium of the experimental pathologist.—J. Garcia-Oller

MOORE, T.: *Dental depigmentation in the rat.* (*Biochem. J.*, V. 37, P. 113, April, 1943.)

Evidence is presented in favor of the view that whitening of the teeth in rats may be caused by a deficiency of either vitamin A or vitamin E. Rats kept on a vitamin A deficiency diet developed whitening of the teeth. These rats were divided in four groups, each group receiving different daily doses of vitamin A. Although the members of each group almost uniformly increased in weight, only the rats in the group given 16 i. u. or more per day showed restoration of teeth pigmentation.

The color of the teeth was restored by administration of vitamin E.

The author also points out the relationship between vitamin A and vitamin E. In the vitamin E deficient animals the vitamin A content of the liver was found to be lower than in the vitamin E non-deficient animals.—C. Foderaro.

MISCELLANEOUS

BARALDI, ALBERTO AND JACOBO BENZADON. *Omphalalgias.* (*Rev. Assoc. Med. Argentina*, V. 57, P. 488, 1943.)

Causes of pain in the umbilicus are considered. Painful inflammation may result from the presence of foreign bodies, calculi, skin inclusions or accumulation of sebum. Umbilical fistulae capable of causing pain may communicate with Meckel's diverticulum or with the bladder through the urachus. Omphalalgia may also be due to small benign tumors, or metastases of malignant tumors, particularly from the stomach. Finally, small umbilical hernias are often overlooked and treatment is directed toward the stomach, intestine, liver, or other viscera: 26 cases were treated by omphalectomy, with good results.—Courtesy Biological Abstracts.

A Review of the Role of the Biliary System in Atrophic Arthritis

By

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THAT the biliary system is related to atrophic arthritis in some patients is a matter of common observation; but the mechanism of this interrelationship is a subject which is not so obvious.

Our attention was focused on this subject by observations of a patient in whom a cholecystectomy had been performed by reason of cholelithiasis, who returned a year later to state that she was not only free from her digestive complaint but from her rheumatism as well. The operation had cured both her gall bladder syndrome as well as her chronic atrophic arthritis.

We have observed this phenomenon numerous times during the years, yet have hesitated to draw hasty conclusions from some scattered cases, bearing in mind that the coincidence of therapeutic results in a patient is apt to attract attention and may simulate the results of cause and effect.

Our studies in this group of patients have been incidental to the study of patients with cholelithiasis in whom the rheumatism was a coincidental ailment. In view of the wide spread incidence of rheumatism, the study of any group of patients will contain a definite ratio of arthritic patients; also it must be borne in mind that relief from any severe bodily ailment as cholelithiasis is apt to be followed by some relief in every other coexisting disease including rheumatism, hence there is definite need for caution in drawing hasty conclusions. Nevertheless there is reason to believe that there exists some relationship between cholelithiasis and atrophic arthritis in some patients.

The study of any small series of patients, no matter how carefully observed, is inadequate to draw conclusions from in a disease as wide spread as rheumatism is, hence we will approach the problem from a review of the literature.

Definitions and Classification

The terms "rheumatism" and "atrophic arthritis" are employed in the commonly accepted sense in this article as well as in many other articles. Indeed it is difficult to find exact definitions for these terms. Hench¹ states that the term "rheumatism" is admittedly a poor term yet remains the best word by which to refer to the group of diseases characterized largely by pains in the joints, ligaments and muscles.

The following classification of the arthritides was adopted in 1941 by the American Rheumatism Association:

- (1) Specific infectious arthritis (organisms known);
- (2) Arthritis of rheumatic fever;
- (3) Rheumatoid arthritis (synonyms: atrophic,

proliferative and chronic nonspecific infectious arthritis, Still's disease, Marie-Strumpell spondylitis);

(4) Osteoarthritis (synonyms: degenerative joint disease, hypertrophic, senescent arthritis);

(5) Arthritis of immediate traumatic origin;

(6) Arthritis of gout;

(7) Arthritis of neuropathic origin (Charcot's) joint;

(8) Neoplasms of joints;

(9) Miscellaneous forms (or arthritis associated with other diseases).

By atrophic arthritis is understood that form of arthritides called rheumatoid arthritis by the American Rheumatism Association. It is a systemic disease chronic in course characterized in the later stages by atrophic or wasting appearances of the joints and the muscles, combined with disturbances of other tissues. It occurs more frequently in women than in men, and commonly in the third, fourth and fifth decades of life. The chief symptoms are pain in the joints and disturbances in the locomotor system; also constitutional symptoms as fatigue, secondary anemia, loss of muscular power, disturbances in the nervous system, various gastrointestinal dyspepsias and often a toxic involvement of the liver.

Biologic Considerations

Chronic arthritis is one of the most wide spread diseases known to man. It exists in all strata of society and in all races. It exists in civilized man and in primitive man. It also exists in a wide range of mammals both domestic and wild, carnivorous and herbivorous. The disease in no sense can be regarded as having developed since man became civilized; it goes back as far as the history of man can be traced, and even before man's appearance on earth. Direct evidence points to its existence in earliest primitive man; although without doubt the social complex of civilization has modified its pathology, symptomatology and clinical course. Further there exists evidence in the skeletal remains of prehistoric monsters that arthritis existed among the great dinosaurs millions of years before man's arrival on earth (Moodie)²; and man coming along in the evolutionary cycle acquired chronic arthritis as an inheritance from his ancestors as an expression of their conflict with their environment.

A consideration of the universal distribution of chronic arthritis both in man and in beast, civilized and primitive, domestic and wild, carnivorous and herbivorous, extant and extinct will moderate any preconceived prejudices we may have on the etiology of the disease and assist us to take a broad biologic approach to the problem.

If rheumatoid arthritis is a broad biologic prob-

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lem so is cholecystic disease. Gallstones and infection of the gall bladder are known to occur spontaneously in numerous animals. Gauss and Davis³ have reported their observations on 2067 slaughtered cattle coming to a packing plant in Denver in which they found an incidence of gallstones in 1 percent of the animals. The stones occurred in both sexes, although most of the stones were found in adult females that had been pregnant. Other forms of cholecystic disease which they observed are liver abscess, fluke infestation, papillomatous nodules in the gall bladder, diverticula of the gall bladder, cholecystitis.

Bacteriologic Studies

The etiology of arthritis is in anything but a satisfactory state today. In 1912 Billings⁴ drew attention to the importance of focal infection in systemic disease and immediately there poured forth a veritable avalanche of observations on the alleged etiologic importance of various microorganisms especially the streptococcus. Indeed at one time the streptococcus was considered to be the "cause of all evil", rheumatism included.

In 1916 Rosenow⁵ a contemporary of Billings and a great champion of the pathogenicity of the streptococcus reported a series of cultures on the bile obtained at operation in which fifty-five percent of the cultures were positive with the streptococcus predominating, while some other organisms were obtained in lesser amounts as *B. coli*, *B. welchii*, *B. proteus* and diphtheroids. In 1922 Drennan⁶ reported his studies on 100 specimens of operative bile. He did not find the high incidence of streptococci reported by Rosenow. Drennan reported that the predominating organisms were *B. coli* and staphylococcus. In 1924 Blalock⁷ reported that 58 percent of his series of 270 specimens of operative bile gave positive cultures in which *B. coli*, staphylococcus and *B. typhosus* were the predominating organisms. In 1925 Johnson⁸ reported his study of the operative bile in 100 patients in which he obtained 32 percent positive cultures with the streptococcus and *B. coli* predominating. Numerous other observers reported their findings about this time with more or less similar results. In 1935 Hanssen and Yurevich⁹ made an exhaustive review of the bacteriologic studies on the bile and added their own study on 104 patients with chronic cholecystitis in whom they made cultures not only on the bile but also the wall of the gall bladder, the cystic lymph node and the incidental calculi. They obtained positive cultures in 33 percent of their 104 patients in whom they found the gall bladder to be the most frequent site of infection, even more frequently than the bile and other tissues. When infection was present they obtained a pure culture in 95 percent of the cases with the streptococcus and *B. coli* predominating and the following organisms in lesser frequency, staphylococcus, *B. typhosus*, *B. welchii* and *B. proteus*. Willard and Strawbridge¹⁰ believe that there is ample proof that the gall bladder may act as a focus of infection in arthritis. They state that various workers have reported positive cultures from gall bladder bile in from 19 to 54 percent of cases and from the wall in from 25 to 84 percent. Rehfuß

and Nelson¹¹ state that in a composite review of 2,162 cases of cholecystitis studied bacteriologically following cholecystectomy more than 45 percent yielded positive cultures from the wall of the gall bladder and more than 29 percent from the contents of the gall bladder. Judd and Hensch¹² state that in some cases cholecystitis and arthritis may bear an indirect relationship in which both arise from some other primary focus. They report a follow-up study of 46 cases of atrophic arthritis in which cholecystectomy had been performed showing complete relief of the symptoms or arthritis in five patients, marked improvement in eleven patients and moderate improvement in eight patients. In all 52 percent of these arthritic patients in whom the gall bladder had been removed showed some improvement in their arthritis following cholecystectomy. They conclude that when definite surgical indications for cholecystectomy are present, it is justifiable to urge surgical intervention in the hope that the arthritis may be definitely benefited.

The bacteriological examination of the bile presents certain obvious difficulties, the chief one of which is contamination by the gastric and oral contents. To avoid this difficulty, Twiss¹³ and his associates devised a special duodenal tube with an opening which they encapsulated to prevent contamination. Employing this special tube they studied a series of 120 patients with biliary disease in whom indications existed for operative procedures. They obtained sterile cultures in 75 patients practically all of which were also sterile at the time of operation; whereas in 28 patients they obtained positive cultures which also agreed with the cultures made on the operative bile; while 17 patients had positive cultures preoperatively and sterile cultures at the time of operation. With their technique they were able to confirm 83 percent of their preoperative cultural findings. They concluded that the gall bladder if diseased is frequently infected and as such can act as a focus of infection, and they believe that many patients with atrophic arthritis improve upon the removal of their diseased gall bladder.

Peers¹⁴ studied seventy-one patients with arthritis both atrophic and hypertrophic in whom he observed that insufficiency of the gall bladder is a frequent occurrence in the rheumatic syndrome. He is of the opinion that a gall bladder visualization should be made in all patients suffering with chronic arthritis.

Etiology of Atrophic Arthritis

It is still generally assumed that atrophic arthritis results from an infection of some kind, but the identity of the specific microorganism remains undetermined. The streptococcus viridans and hemolyticus once strongly suspected have been acquitted by the observations of Cecil, Angevine and Rothbard¹⁵ who were able to produce experimental arthritis with these organisms, but they were also able to produce similar types of arthritis with staphylococcus aureus, pneumococcus, and paratyphoid A. Cecil¹⁶ concludes "that the time has come for a complete reevaluation of the focal infection theory".

Virus like bodies have been observed and isolated in the tissues and exudates of arthritic lesions, by

Schlesinger, Signy and Amies,¹⁷ yet these have not been shown to possess the capacity to produce arthritic lesions.

At other times a pleuro-pneumonia-like organism was described by Sabin,¹⁸ Swift and Brown¹⁹ as the causative factor in atrophic arthritis, yet controlled experiments failed to substantiate the claims.

One after another various organisms and viruses have been mentioned as the cause of arthritis, yet one after another they were shown to be baseless claims. Today it may be said that there is no accepted etiologic cause of atrophic arthritis. Indeed Pemberton and Scull²⁰ state that there is no specific agent capable of identification by means now available for direct examination or growth on culture media which is uniformly found in arthritics, and it is only on indirect circumstantial evidence that any specific microorganisms can be incriminated.

Chronic arthritis however does produce certain definite changes in the body. These are pathologic alterations, humoral reactions and clinical expressions. The pathologic changes are local reactions as inflammation, lymphoid infiltration, degenerative changes; the humoral reactions occur in the blood stream as antibody formation, formation of agglutinins precipitins, fibrinolytics and increased sedimentation rate; the systemic reactions are fever, leukocytosis, fatigue, secondary anemia, etc. The characteristic pathologic alterations are proliferative changes in the synovial membrane and marrow characterized by focal collection of lymphocytes also by subcutaneous nodules caused by collections of lymphocytes about central areas of necrosis. All these point to an inflammatory basis of chronic arthritis; they suggest an infection but do not prove it. Cecil¹⁶ suggests that the joints may not be actually infected; rather they become sensitized in some way to the products of streptococcal metabolism.

Interrelationship between the Biliary System and Arthritis

The biliary system is interrelated with the problem of arthritis in two main ways, first there is a probable bacterial connection, second a metabolic relationship. The bacterial relationship has occupied the center of attention in the past on the assumption that the gall bladder might serve as a focus of infection to the joints. An enormous literature has accumulated on this subject, with the various authors arguing the merits of their several techniques to insure the recovery of the proper organisms from the biliary contents or the walls of the gall bladder; and now it is beginning to be admitted that the specific etiologic organism of arthritis remains unknown. However these studies have not been in vain. They have contributed much to the nature of cholecystic diseases.

The theory that an infected gall bladder can act as a focus of infection for atrophic arthritis is not being rejected; at the present it simply has not been proven either bacteriologically or experimentally; although clinically the evidence seems to point in that direction. This is a problem that remains to be clarified in the future.

The metabolic relationship between the biliary system and arthritis is the second relationship. Very much less has been written on this subject because it is still largely conjectural at this time. This metabolic relationship is based on certain humoral and chemical phenomena which at present are only partly known and not measurable by instruments of precision. However with improved chemical methods which are advancing rapidly, we can look forward to improved knowledge along these lines in the near future.

One of the first and rather astounding observations on the metabolic relationship is the influence of jaundice on arthritic patients. One would expect that an arthritic patient would be made worse when burdened with the additional toxemia of jaundice; yet the contrary is true. When an arthritic develops jaundice, he tends to become symptom free of his arthritis. He loses much of the pain and swelling of his joints for the duration of the jaundice. Such remissions have been known to have lasted for three months.

Obstructive jaundice results in toxic hepatitis. Because of this phenomenon Hench¹ raises the question whether rheumatoid arthritis is caused by some hypohepatia or hyperhepatia which becomes temporarily corrected during the presence of the toxic hepatitis. According to him this phenomenon proves that rheumatoid arthritis is not an inherently irreversible reaction.

There is another possible explanation to this phenomenon, namely that incidental to the presence of jaundice, the liver elaborates some chemical into the blood stream which exercises a beneficial action on arthritis comparable to the relief which epileptics obtain in starvation acidosis where an ether-like radical is elaborated from diacetic acid which has a sedative action on the central nervous system.

This interesting observation is of little help at present in the analysis or therapy in the metabolic relationship because for the present there is no known practical way to reproduce the effects of clinical jaundice.

Jaundice is a very dramatic episode in the disturbances of the biliary system, but it is only one of many chemical imbalances that can happen to the body from dysfunctions of the liver. When one considers the multiple chemical activities engaged in by the liver, the number of potential chemical imbalances are staggering.

The liver we recall is normally engaged in (1) the synthesis of bile, (2) glycogen function and maintenance of blood sugar level (3) urea formation and excretion, (4) storage and activation of fats, (5) iron metabolism, (6) detoxifying function for many waste products from the bowel and other noxious substances and the conversion of some of these into ethereal sulphates and their subsequent excretion, (7) bactericidal action on intruding bacteria, (8) excretion of cholesterol, (9) blood and iron reservoir, (10) part of the reticulo-endothelium system, (11) interrelationship in the endocrine system, (12) etc. Any one or any combination of these functions may become impaired and

produce a chemical imbalance and produce remote effects in the body.

Our laboratory tests for liver function are extremely crude today. Cholecystography is the best test we have for liver function. Examination of the removed bile is good; the Icterus index test is helpful at times, but it usually tells us what we already know clinically. There are numerous chemical tests as the Van den Bergh test, the galactose test, various dye tests, etc., but these have a rather limited use clinically. There is no way to measure the flow of bile into the intestine under basic conditions. There is no way to measure the chemical imbalances of the liver in a person who overburdens it with excess food, or a badly balanced diet or a deficiency diet or an excessively greasy meal. There is no instrument of precision to measure the amount of biliousness complained of by a patient, yet all these are chemical imbalances which affect the body.

Hench¹ states categorically that it takes something more than an infected focus to produce arthritis. C. H. Brown²¹ has observed focal infection in 63 percent of 239 psychiatric patients none of whom had arthritis.

Recently Selye²² and his associates have opened a new line of investigation by observing that experimentally in the rat an overdose of desoxycorticosterone acetate produces polyarthritis which histologically resembles that seen in acute rheumatic fever, which according to him seems to indicate that the adrenal cortex may play an important role in the pathogenesis of rheumatic fever. This work is extremely interesting in opening a new angle to the metabolic concept in the etiology of arthritis. It is extremely useful in shifting the center of attention from focal infection to the metabolic concept. However later it may be shown that the two concepts are interrelated.

Diagnosis of Biliary Disease

The implication that disturbances in the biliary system are involved in the pathogenesis of atrophic arthritis demands that we recognize those disturbances in the liver.

Considerable progress has been made in the recognition of gall bladder pathology, while many disturbances of the liver remain a matter of clinical interpretation without benefit of precise diagnostic methods.

There are now available four main methods of inquiry into biliary diseases. These are: (1) clinical signs and symptoms, (2) nutritional analysis, (3) cholecystography, (4) laboratory methods, particularly the examination of the bile.

Clinical signs and symptoms include the manifestations of biliary colic and gall bladder dyspepsia. Biliary colic is pathognomonic of cholelithiasis subject to confirmation by differential diagnosis. Gallbladder dyspepsia is suggested by the syndrome of "fair, fat, forty and belching gas"; also by fullness in the epigastrium after meals, intolerance for certain foods as onions, cabbage, radishes, cauliflower, etc.; flatulence, coated tongue, constipation, bitter taste, biliousness, etc.

Nutritional analysis is a distinct analytical method, and a very useful one in the hands of trained observers. The patient seldom volunteers nutritional information. It must be ascertained. Many patients do not know

whether the diet that they are eating is an adequate diet or not. Some patients have a negligible appreciation or even a contempt for the principles of a balanced diet, and few patients have any appreciation at all of their energy needs as influenced by the disabling influences of arthritis; while too often the appetite and the pocket book are the sole criteria for the food intake.

Cholecystography is at present the most exact diagnostic procedure we have for obtaining information concerning the morphology and function of the gall bladder. In the diagnosis of gall stones it is surprisingly accurate, only the smallest gravel now escape detection and only when there are a few of them. Cholecystography also gives information as to the size, shape, configuration and alterations in contour. The filling and emptying time and ability to concentrate the dye gives valuable information as to its behavior.

Non-visualization indicates a severely diseased gall bladder; poor visualization indicates impaired function, likewise delayed filling and emptying time are indicative of disturbed function.

Examination of the bile removed by the Lyon method is helpful in evaluating the degree of impaired function or the presence of infection. Willard and Strawbridge¹⁰ consider the following signs indicative of gall bladder disease; namely the absence of B bile of Lyon, the presence of bile stained mucus, pus cells, or columnar epithelium, the presence of calcium, bilirubin pigment or cholesterol pigment.

Treatment of Biliary Disease

The treatment of a diseased gall bladder in the presence of arthritis is not materially different than it would be without the complicating arthritis.

The writer is thoroughly in accord with opinion expressed by Judd and Hench¹² who have stated that when surgical indications exist for cholecystectomy, there is reason to believe that the arthritis will be definitely benefited by the removal of the gall bladder. Numerous observers have recorded that the removal of a focus of infection in some patients is sufficient to swing the balance toward recovery. This observation has been pretty well established clinically in spite of the lack of proof of a specific etiologic factor in atrophic arthritis.

However just what constitutes the indications for cholecystectomy is a matter that is subject to wide interpretation. For our part we have been conservative in what we consider to be "indications". We consider the following to be indications for cholecystectomy: (1) cholelithiasis giving rise to symptoms, or complicated by arthritis or other disease, (2) a non-visualized gall bladder which does not respond to treatment, (3) a persistent gall bladder dyspepsia after treatment.

Medically much can be done to improve the well being of the patient with gall bladder disease with or without arthritis. In our experience some patients have shown as gratifying an improvement by adequate medical management as by surgical procedures; besides it is the last hope for the cholecystectomized patient.

Medical management aims to assist the impaired

physiology of the biliary tract by whatever methods it can. There is no specific cure, neither is there any specific diet for the complicating arthritis. It considers in the first place, the nutritional requirements of the patient. Many patients with biliary dyspepsia manifest nutritional imbalances. The arthritis often further restricts his nutritional needs by his enforced curtailment of activity; so that his actual caloric needs are often less than that of the average person. Any intake of food above the actual requirement simply imposes a needless burden on the digestive tract, the liver and gall bladder included. So in the first place, the energy needs of these patients are usually placed at 1800 to 2200 calories, seldom above this figure. If the patient is obese, it is further reduced to 1200 calories.

It is amazing how often we encounter a cholecystectomized obese person who tells us that he has been told to eat any amount of any kind of food that he desires as the cholecystectomy had cured him of all of his troubles.

The foods considered to be digestive irritants, as coffee, onions, cabbage, etc. are removed from the diet or at least markedly restricted. Inquiry is made into the history of allergy, and food of high allergy index are likewise removed from the diet as shell fish, chocolate, etc. A carefully balanced diet is then planned which supplies the basic needs of protein, fat, carbohydrates, minerals, vitamins and roughage. The energy needs of the person are not exceeded. This diet is not a fixed diet. It is made elastic by the varying demands of the patient by such conditions as age, weight, nutritional status, allergic manifestations, fever, infections, cardiac disease, arteriosclerosis, achylia, etc.

Therapeutic biliary drainage has a definite place of value in the management of these patients. The popularity of this procedure has swung from one extreme to the other. At first it was employed extensively, then when it failed to cure a lot of chronic infected gall bladders it was discarded as tried and found wanting. Nevertheless it seems to the writer to be just good common sense to remove infected bile periodically from a diseased gall bladder in the same spirit that one removes infected urine from the urinary bladder periodically.

Cholagogues have a useful place as these promote the free flow of bile and assist in the drainage of the gall bladder; also they definitely enhance the well being of the patient, besides being of definite help in the particular type of constipation suffered by many of these patients. Elsewhere we²³ have discussed this so-called "biliary constipation".

Physiotherapy, particularly diathermy treatments to the gall bladder, has been observed to be helpful in some patients.

The systemic treatment of arthritis is employed as indicated, but the discussion of this is beyond the scope of this paper.

SUMMARY

1. The biliary system is related to the mechanism of atrophic arthritis in some patients.
2. The mechanism of this interrelationship has not been fully analyzed.
3. There are two probable interrelationships (1) bacterial, (2) metabolic.
4. Atrophic arthritis is a universal disease existing both in man and beast, both wild and domesticated, carnivorous and herbivorous, civilized and primitive, extinct and extant; hence any approach to the problem must be along broad biologic lines. Cholecystic disease is likewise a broad biologic problem.
5. The etiology of atrophic arthritis is unknown today, although it is commonly considered to be an infection originating in foci elsewhere in the body; yet focal infection alone does not produce atrophic arthritis.
6. Bacteriologic studies of the bile and gall bladder in cholecystic disease show that about one third of these yield pathogenic bacteria.
7. The mechanism of the beneficial effects of jaundice on arthritis is unknown and requires study.
8. Methods of study in cholecystic disease with or without complicating arthritis are (1) clinical manifestations, (2) nutritional analysis, (3) cholecystography, (4) laboratory methods, especially the examination of the bile.
9. Clinically the medical management and the surgical removal of the diseased gall bladder is frequently followed by marked relief from the symptoms of arthritis.
10. This subject requires further study.

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Enzyme Treated Milk in the Dietary Management of Patients with Peptic Ulcer

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MILK is the food which best answers the requirements of the patient with peptic ulcer. It is free from substances (extractives) that stimulate an excess acid secretion; its carbohydrates are easily digestible; its proteins call forth the least amount of acid; its fats are well tolerated; and when given in moderate amounts and properly modified, milk quickly leaves the stomach. Without some modification, ordinary pasteurized milk is poorly tolerated by many ulcer patients, particularly by those with a high degree of hyperacidity. To attain its maximum therapeutic value, milk has to be modified for the individual patient. Some tolerate it better raw, others when it is boiled. Some are more comfortable and do better with whole milk, others with milk and cream mixtures, and still others prefer skimmed milk. In some instances, dilution of ordinary milk with Vichy water, lime water or other mineral water is helpful. Frequently a modified milk, peptonized milk, soft curd, or malted milk, can be taken when ordinary milk disagrees with the patient. At times a fermented milk (Koumiss, buttermilk, etc.) is better tolerated than the usual pasteurized product. Fermented milk, however, is rarely advisable as part of a peptic ulcer diet because of its increase of gastric acidity in an already highly acid stomach.

When ordinary milk is not tolerated, the provision of a satisfactory substitute is often difficult. The multitude of milk modifications that have been proposed and are being used with variable success attest to this. Frequently modified milks differ so much from ordinary milk in chemical and physical character that they do not act as good substitutes. The fermented

milks, especially, are undesirable because of their added acidity. Recently, an enzyme treated milk* has been introduced as a satisfactory substitute for ordinary milk, for drinking without further modification.¹ Glynn² and Blatt and his associates³ have reported upon its use as an infant food. This enzyme treated milk, Enzylac, is prepared by the addition of a pancreatic proteolytic enzyme to fresh, market milk, before pasteurization. It retains the taste, appearance, the mineral and vitamin contents of ordinary milk. It differs from ordinary pasteurized milk in that when acted upon by gastric juice, a soft, friable curd of low tension results, which is rapidly digested and expelled from the stomach. These soft, smaller curds of the enzyme treated milk, in contrast to the harder and larger curds of ordinary milk, cause less peristaltic activity and thus reduce the mechanical burden of the stomach. Since excellent clinical results were obtained from feeding this enzyme treated milk to the infants in the Children's Division of the Cook County Hospital, it seemed desirable to investigate Enzylac as a substitute for ordinary milk in the dietary regimen of peptic ulcer patients.

Material and Method

1. The study of the enzyme treated milk was conducted in two phases. The purpose of the first phase was (a) to determine the comparative efficacy of enzyme treated milk and ordinary milk as acid modifiers, and (b) to compare their curd formation by measuring the size and amounts of curds left in the stomach one hour after the ingestion of 200 cc. of enzyme treated milk and of ordinary milk, respectively.

2. The second phase of the investigation was essentially the clinical observation of the subjective and objective effects of enzyme treated milk fed to ulcer patients, who had shown a poor tolerance to ordinary pasteurized milk.

Twenty-four hospitalized patients, from 24-60 years of age, with active peptic ulcer, were studied. On the first day of the investigation, a Rehfuess tube was

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* This milk, perfected jointly by the American Seal Kap Corporation and the Armour Laboratories, is marketed as "soft curd milk produced by the enzylac process" or under the trade name of Enzylac.

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passed into the stomach of the fasting patient and the stomach contents aspirated, measured and tested for free and total acidity with Topfer and phenolphthalein reagents.* Aspirations were repeated at fifteen minute intervals, and the specimens titrated for free and total acidity. The results obtained were plotted as a curve. Aspirations were performed for two hours (8 specimens) or until no more gastric juice was obtained.

The following day, the tube was again passed, the fasting juice aspirated and tested, and the patient given a test meal consisting of four arrow root crackers and 200 cc. of water. The gastric contents were aspirated every fifteen minutes and the specimens titrated for free and total acidity. On each of the succeeding four days, 200 cc. of ordinary milk or 200 cc. of enzyme treated milk were used as the test meal and the aspirations and titrations were carried out as before. The curves of both combined and free acidity were plotted for comparison.

Some of the same patients were used for the investigation of the curd formation. In this procedure, each patient was first aspirated and then received 200 cc. of either ordinary milk or of enzyme treated milk. At the end of one hour, he was placed on his left side, his head inclined downward, and his stomach aspirated. The aspirated gastric contents were measured, their gross appearance and the amount and physical characteristics of the curds, i.e., size and consistency recorded.

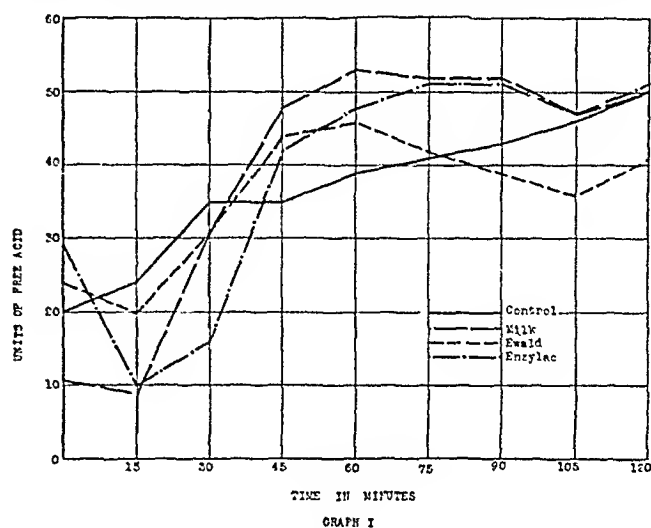
For our clinical phase, we used peptic ulcer patients who tolerated ordinary milk poorly, as evidenced by complaints of nausea, epigastric distress, belching and/or bloating following its ingestion. These patients were given enzyme treated milk instead of the usual milk and cream mixture, and were then questioned daily about their symptoms. As the study progressed, other than ulcer patients who tolerated ordinary milk poorly were included in this study. More than one hundred patients, about one-half of them with peptic ulcer, were observed.

Results

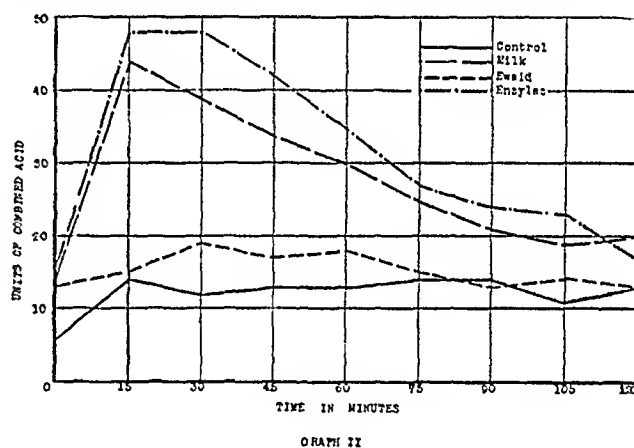
The results of the tests in Part 1 are shown by Graphs 1, 2 and 3. From them it is apparent that the averages of the free acid values were lower after enzyme treated milk than after ordinary milk. Moreover, what is even more important is that the average combined acidity was definitely higher after enzyme treated than after ordinary milk. Enzyme treated milk caused a lower free acidity in 28% of cases and a greater combined acidity in 40% of cases. Moreover, it was observed that the acidity curves of Enzylac were "smoother", i.e., had less "valleys" and "peaks" than the curves of plain whole milk.

The results of the curd experiment confirmed the observations of other investigators. In 70% of the cases the curds of the enzyme treated milk were smaller, softer, more friable and tended to float on the surface of the aspirated gastric juice. The intimate mixing of the enzyme prepared milk with the gastric juice was evident from the milky appearance of the aspirated gas-

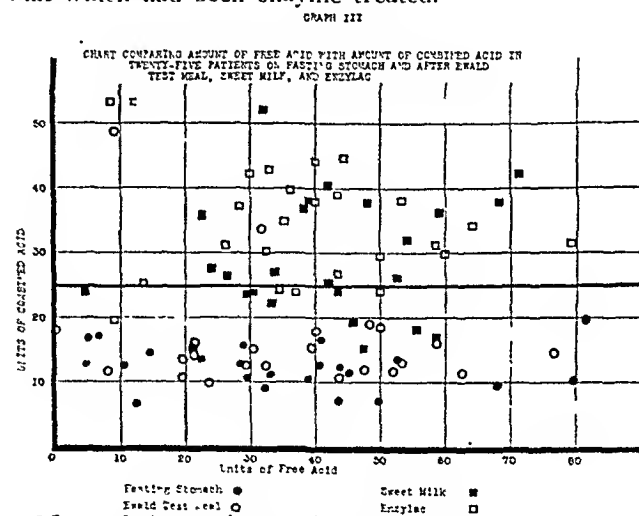
tric contents obtained following the ingestion of Enzylac. In comparison, the curds of ordinary milk were in



most instances larger, harder and lying at the bottom of the glass container, while the aspirated gastric juice



was only slightly opaque; an evidence that ordinary milk did not mix with gastric juice as well as did that which had been enzyme treated.



Most of the patients with symptoms of intolerance to ordinary pasteurized milk were able to take enzyme

* The acidity of a small number of cases was determined as to pH value with the potentiometer.

treated milk without discomfort. The many and variable symptoms of milk intolerance began to disappear within a few days and the patients became less complaintive and more energetic. Frequently, enzyme treated milk gave relief when other modified milks (soft curd, or malted milk) failed to do so.

Discussion

There is no controversy about the necessity of a dietary regimen in the treatment of peptic ulcer, although there is quite a variance of opinion as to the most effective medicinal treatment. A perusal of the literature on the treatment of peptic ulcer reveals, however, that until recently some of the dietary regimens were either too strict or too empiric and for these reasons have been gradually discarded. In the past few years, following the advances in our knowledge of biochemistry, nutrition and dietetics, the principles and basis for the dietary treatment of peptic ulcers have been better understood. Treatment has improved with the intelligent application of this knowledge.

The main object of the dietary regimen in peptic ulcer is to furnish a variety of foodstuffs which bring about local conditions favorable to the healing of the ulcer and, at the same time, furnish adequate nourishment. Such foods must be easily digestible, and cause a minimum of gastric activity. They must reduce gastric acidity by preventing excessive secretion, and (2) by combining freely with the gastric juice as secreted. These food substances should be so combined that they contain adequate amounts of proteins, carbohydrates and fats in the proper proportions. Finally, the diet must be planned to contain an adequate amount of the essential minerals (iron, calcium, phosphorus, potassium, sodium, chloride) and an excess of vitamins. A diet thus arranged, limits further damage to the stomach and reduces to a minimum any disturbance of the processes of repair.

In planning an ulcer diet, one should not have in mind primarily the chemical angle, i. e., the acidity decreasing or combining power, but the physical nature of the foodstuffs and the manner of their serving must be considered. The diet should be so planned that besides decreasing the acidity, it will also reduce motor activity of the stomach. To accomplish this, the consistency of the food must be such that it will pass out of the stomach with a minimum of effort on the part of this organ.

Large food particles, when forced against the pylorus, will irritate it, lead to an increased activity of the antrum and increased peristalsis of the entire stomach. Food in a fluid or semi-fluid state passes rapidly from the stomach. Foods which, when ingested remain fluid or semi-fluid, limit the motor activity and thus fulfill a therapeutic indication.

Of the various foodstuffs, carbohydrates (if taken in an easily assimilable form) remain relatively a short time in the stomach. Proteins remain longer and fats the longest. A mixture of the various foodstuffs remains in the stomach according to their proportion. It has also been shown that the fluid parts and softer foods leave the stomach first: the solid residue is ex-

pelled last. The violent contractions of the stomach to expel this residue are frequently coincident with the onset of post-prandial ulcer pain. Based upon this observation, it has been suggested that this muscular effort (tension) may be as much responsible for the pain of gastro-duodenal ulcer as the high free hydrochloric acid.

Since milk and milk products form an important part of the dietary regimen of a peptic ulcer patient, the management of such an individual becomes a difficult task if an intolerance to ordinary pasteurized milk is present. None of the previous milk modifications which have been produced for use in this condition have proved uniformly successful. It was, therefore, of more than academic interest to test an enzyme treated milk as a substitute for ordinary milk in the treatment of patients with peptic ulcer, especially since neither the nutritive value nor the mineral content of the new modification were decreased although the protein was denatured and the physical character of its resultant curd changed.

The beneficial effects of this enzyme treated milk may be attributed to both its chemical and physical properties following its admixture with the gastric juice. Under the former, one must include mainly its tendency to increase the combined and decrease the free acidity. This is of value if one considers the acidity as a factor in ulcer pain. Its transformation into small, soft curds, which leave the stomach rapidly make it a good nutritive substance for ulcer patients because this property minimizes the peristaltic activity of the stomach and thus reduces tension, which by some is considered the cause of ulcer pain. Furthermore, keeping in mind some of the theories on food allergy,⁵ one might attribute the beneficial effect of Enzylac in patients with milk intolerance, to its preparation with a pancreatic concentrate high in tryptic value.

Enzyme treated milk, however, should not be considered only a milk substitute in patients with peptic ulcer who do not tolerate ordinary milk; it should rather be considered as the ideal milk for most ulcer patients. Both the secretory and motor phases of gastric activity in peptic ulcer are beneficial by its use. From the reports in the literature and our own observation, enzyme treated milk seems to meet the requirements of a good food for peptic ulcer patients.

Summary and Conclusions

1. Milk fulfills the requirements of an ideal food for the ulcer patient. In many instances, however, ordinary pasteurized milk is not well tolerated and modified milks must be substituted.

2. A recently introduced enzyme treated milk, Enzylac, possesses the same nutritive value and mineral content as ordinary pasteurized milk. It, however, has the advantage over the latter in that it causes a higher combined and a lower free acidity, and in that softer, smaller and more friable curds result from its ingestion than follow the intake of ordinary pasteurized milk. The friable curds of Enzylac are expelled more easily from the stomach than the tougher curds of ordinary milk.

3. Enzyme treated milk is well tolerated by some patients who have an intolerance to ordinary milk.

4. Because of its chemical and physical properties, enzyme treated milk appears superior to ordinary milk

in the dietary regimen of peptic ulcer patients.

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The Influence of Phenolphthalein Ingestion on Red Blood Cell Resistance to Hemolysis

By

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THE literature on phenolphthalein for a few years after it was introduced as a laxative contains several references^{1, 2, 3, 4} stating that hemolytic and bleeding phenomena occasionally follow the ingestion of phenolphthalein. Some of these references were quoted so often that it made it appear that hemolytic processes are a common occurrence after phenolphthalein.

Surprisingly, such reports became less, the larger the use of the substance. However, a few years ago such a report appeared which was later found to be groundless;⁵ and quite recently the question arose whether the administration of phenolphthalein to patients receiving sulfonamides might not be productive of hemolytic phenomena.

In our investigations on the action, absorption and elimination of phenolphthalein we failed to observe any hemolytic action on normal individuals or on patients. Furthermore, in view of the recent finding that phthalic acid is the active principle in the synthetic vitamin K preparations, the opposite would be expected.⁶ Nevertheless, a study was planned to determine whether hemolysis of red blood cells or bleeding is more likely to occur when animals received phenolphthalein and sulfanilamide together.

Method

A small number of rats (19) from a similar strain were used. Five animals served as controls; three were put on the usual rat diet containing 2% white phenolphthalein; two on a similar diet containing 2% yellow phenolphthalein; three on a similar diet containing 2% sulfanilamide; one each on a similar diet containing 1% sulfanilamide and 1% phenolphthalein, and 1% sulfanilamide and 1% yellow phenolphthalein respectively; two each on a similar diet containing 2% sulfanilamide and 2% phenolphthalein, and 2% sulfanilamide and 2% yellow phenolphthalein respectively.

After thirty days, two controls, one rat on 2% sulfanilamide, one on 1% sulfanilamide and 1% phenolphthalein, one on 1% sulfanilamide and 1% yellow phenolphthalein and one on 2% sulfanilamide and 2% yellow phenolphthalein were sacrificed and the blood tested for resistance to hemolysis.

After forty-two days, one of the controls, one rat on 2% sulfanilamide, one on 2% sulfanilamide and 2% phenolphthalein and one on 2% sulfanilamide and 2% yellow phenolphthalein were sacrificed and the blood tested for resistance to hemolysis.

After sixty days, two controls, one rat on 2% sulfanilamide, one on 2% sulfanilamide and 2% phenolphthalein, one on 2% sulfanilamide and 2% yellow phenolphthalein and one on 2% yellow phenolphthalein

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Discussion

From the above experiments it appears that phenolphthalein alone, when given to rats for thirty to sixty days, does not change the resistance of their red blood cells to saponin hemolysis. However, if rats are given 2% sulfanilamide for the same period of time, the resistance of their red blood cells to saponin hemolysis is markedly diminished. Similarly, if rats are given mixtures of either 1% sulfanilamide and 1% phenolphthalein or yellow phenolphthalein; or mixtures of 2% sulfanilamide and 2% phenolphthalein or yellow phenolphthalein, the resistance of the erythrocytes of these rats is also diminished about as much as when sulfanilamide alone is given. There is no increased hemolysis so there is no synergistic effect.

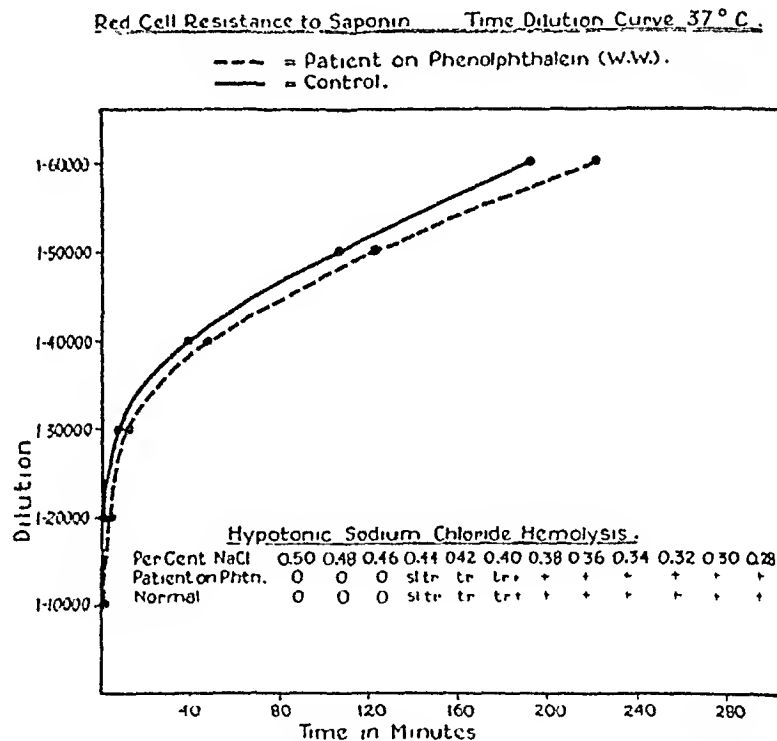
It is therefore concluded that the decreased resistance

to saponin hemolysis of erythrocytes of rats fed sulfanilamide and phenolphthalein mixtures is due to the sulfanilamide. This conclusion seems warranted also because of reports in the literature^{10, 11} and of other experiments which failed to show an increase in urinary urobilinogen following prolonged phenolphthalein ingestion but did show it after sulfanilamide ingestion.

Summary

The resistance of erythrocytes of rats to hemolysis by saponin is decreased when these rats are fed sulfanilamide alone or sulfanilamide mixed with phenolphthalein. The feeding of phenolphthalein alone to rats does not cause any change in the red cell resistance. Hence, any hemolysis that may occur in subjects receiving both sulfanilamide and phenolphthalein is due to the sulfanilamide.

Fig. 3



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The Secretion and Excretion of Bile in Relation to Constipation*

By

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THE secretion of bile has been studied and written about for over 2000 years. It still remains confused, and not well understood.

Horrall¹ has summarized the views held and work done on bile up until 1937. He quotes 2177 references, which indicates the thoroughness of a study which occupied him for over fifteen years. Yet in the last paragraph he says: "The primary purpose of this book has been to state and correlate experimental work that has been done, and to point out the great need for further experimental investigation and clinical observation."

Most students will agree with him when he says: "Methods of investigation which simulate as nearly as possible the conditions normal and pathologic found in the human are quite necessary. When these are developed and carefully controlled, and chemically pure substances are used, we may be able to discover facts. Indirect, inadequate, faulty, and pseudo-scientific work almost obscure the entire horizon in this field." (page 19).

Bile is both a secretion and excretion. A secretion is necessary for normal physiological processes. An excretion is a waste product, which if not eliminated may be toxic. Administered bile is largely excreted.

The volume of bile normally secreted by man in 24 hours is estimated between 530 cc. (Wittich) and 940 cc. (Mayo-Robson). The volume secreted may be found by means of a fistula, either temporary or permanent. Pfaff and Balch report a case that secreted 525 cc., and another (a woman) who secreted 939 cc., in 24 hours. In these cases no bile was finding entrance into the intestine, and this would tend to diminish the volume secreted. On the other hand, the acids of the chyme act as a stimulus to the formation of bile, and in the absence of bile the chyme may remain longer in the duodenum, and thus act as a stimulus to secrete more bile. The absence of bile thus might act as a stimulus, as will the presence of bile, so it is difficult to get a true estimate. It seems probable, however, that when bile is allowed to enter the intestine the excretion is larger rather than smaller than the volume given (Mathews).

Sabotka² gives an excellent account of bile secretion. He summarizes the objections to the fistula methods of obtaining bile, and says it is quite probable that no fistula method gives accurate results. Like Horrall he stresses the need for a method which simulates the normal method of secretion.

Cholagogues and Cholagogics

Much time has been devoted to studying modifications of bile flow. Sabotka gives a summary of the

drugs studied and the results. Ivy³ et al. also present a summarized table.

Each investigator of the secretion of bile claims some special advantageous technique, from the time of Rutherford to Ivy. Their results are often quite contradictory—which suggests that quite as important as the technique is the condition of the animal or man—that is studied, and the fundamental physiology of bile secretion. Perhaps the greatest error in their results is the claim that bile and bile salts, are the cholagogics par excellence.

Is Bile a Cholagogue?

Much misunderstanding exists concerning the terms "cholagogue" and "cholagogue." The term cholagogue is old, probably used from the time of Hippocrates (430 B. C.). He believed that bile was a common cause of disease; in fact, the cause of practically all illness. Much thought was therefore given to bile and its secretion. It was not until 1722, however, that Deidier made the first biologic experiments with bile. He injected bile into animals and concluded that bile is toxic when given intravenously. When given orally, however, bile causes no illness. (Ref. in Horrall.)

Since the time of Deidier, the experimental study of bile and its secretion has been more or less continuous.

From 1875 to 1879, William Rutherford and collaborators, reported a series of papers on *The Action of Drugs on the Secretion of Bile*. The results of their findings were immediately accepted, and the "cholagogics" recommended by them, used in therapeutics until the present time. In recent times, however, some of their findings have been questioned.

In a synopsis of this work in the Practitioner, 1879, Vol. 23, p. 426, Rutherford says: "The term 'cholagogue' is of necessity a vague one and applicable to any substance that increases the biliary flow, whether by augmenting bile secretion or by exciting contraction in the walls of the bile passages. We have therefore applied the more definite term 'hepatic stimulant' to those substances which we have proven to increase the secretion of bile." This seems to make the distinction for the first time, between the use of the term "cholagogue" and what is now known as "cholagogue".

In 1923 Brugsch and Horstler⁴ used the term "cholagogue" for agents that increase the secretion of bile; the term corresponds to the term "diuretic".

The action of cholagogics and cholagogues is much discussed, and their value disputed. Just when it will be settled remains for the future. Rutherford, whose work was accepted as classic, says of his technique:

"We claim that, by means of a novel and precise method of investigation, we have been the first to place the whole subject of the physiological action of drugs on the bile secreting function of the liver on a

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sound footing, and thus to lay a real foundation for the rational—that is, scientific—treatment of many diseases of this important organ, etc.”

Notwithstanding this feeling of confidence and the list of drugs he gives that will increase the flow of bile, and with which many agree, later workers (Ivy and colleagues) have found negative results by methods which they believe surpass all previous methods. Ivy's emphasis of “methodology” seems like a repetition of Rutherford's claim.

What seems to be a fundamentally important fact, and which has been overlooked by all experimentors studying bile flow—is—that the normal liver excretes bile at a maximum rate, for a 24 hour period. It is impossible therefore to increase this maximal rate in the normal subject. It seems only when the rate is below normal—as in constipation—that a “choloretic” will yield striking increase in bile flow. This would account for the variation in results. It would also account for the fact that in practically no disease do we find a truly cholerrhagic condition.

If one considers the unique site of the liver, on the crossroads of the circulation, it is difficult to see how any drug that is absorbed can fail to have some influence on liver function. Whether such influence is important to health, is needed, or may be used beneficially, is another question.

The question which interests us most is the mistaken, though much asserted statement, that bile is a choloretic or causes an increased “secretion” of bile. Textbooks on pharmacology written, as they must be, without sufficient time to critically examine the evidence for each statement regarding the action of a drug but nevertheless accurately quote investigators who were often mistaken. But even investigators cannot always see the picture in its entirety. Constructive criticism will therefore always have a place.

Textbook statements may be taken as the crystallized opinion regarding the action of bile, cholagogues and choloretics.

Cushman (Edmunds and Gunn, 1936) says: As a cholagogue bile is without rival, but no condition is known in which an increase in the secretion is indicated.

Sollmann (1942) says: Intravenous injection of bile salt increases the rate of bile flow to double or more.

McGuigan (Applied Pharmacology) says: Aside from bile itself, there are few drugs that increase the secretion of bile.

Dixon (Manual of Pharmacology, 1936) defines a cholagogue as a substance which increases the secretion of bile and says: By far the surest and most powerful cholagogue we possess is bile or bile salts.

Goodman and Gillman (p. 794) says: Of all substances which are known to stimulate the secretion of bile (choloretics) bile salts are the most effective.

Horral (260), says: The only real effective stimulant for bile formation is bile or bile salts.

In spite of all these statements, bile is not a “choloretic”. That is, it does not stimulate the *secretion* of bile. All that happens is: that the administered bile is excreted. There is no evidence of any new forma-

tion of bile, or any “stimulation” of the liver.

An illustration from Horral (p. 47) will explain this statement:

“A dog with a bile fistula was fed 21 Gm. of bile salt and the excess output was 13 Gm. This quantitative output is not due to actual increased production but merely is absorption and *re-excretion* of the fed bile salt. Bile salt given by mouth or intravenously has the same effect on bile salt output.”

Bile therefore is not a choloretic, but rather an “anti-choloretic”. It appears that never 100% of the administered bile is recovered, and therefore, it must inhibit the normal formation of bile in the liver. All that is obtained seems to be an excretion of what is administered. This is illustrated also by the results of Ivy et. al.

Schmidt, Beazell, Atkinson and Ivy fed dogs 5 Gms. of bilron, dechacid, ketochol, and decholin. The increase in the volume of bile excreted was 75%, 50%, 144%, and 25% over a three day period. The cholate change was 126%, 4%, 28%, and 36%. They conclude: “The conjugated acids of ox bile (bilron and dechacid) are the most satisfactory agents for inducing ‘choleresis’ in the dog. Such preparations are true choloretics, i. e., they produce increased flow of bile and increased elimination of biliary constituents.”

We agree that there is an increased flow of bile, and to that extent they are “choloretics”, but that there is an increased “secretion” of bile acids is quite misleading.

The results as given by these authors are stated as follows:

		24 hr.		24 hr.	
		Normal Bile	Bile Volume	Cholates Before	Cholates After
Bilron	5 Gms.	114 cc.	198 cc.	1.420	3.312
Dechacid	5 Gms.	123	185	1.348	1.405
Ketochol	5 Gms.	106	259	1.426	1.021
Decholin	5 Gms.	117	146	1.536	.976

The first two only, increase the cholates. From a physiological point of view, the cholates are the most important constituent of the bile, and mere increase in volume—i. e. a watery bile, no matter how large, can not properly be looked on as an increase in bile. However in no case does the increase in volume correspond to an actual increase.

In the case of bilron, the normal volume of bile is 114 cc. This would contain about 2 Gms. of bile acids. 5 Gms. of bilron at the same ratio, should produce at least 200 cc. of bile. If the normal flow therefore, continued during the administration of bilron we should expect at least 314 cc. bile. Instead however, 198 cc. is obtained.

Also with the cholates—the normal is 1.420 Gm. The amount of bilron given if converted into bile acids should give an increase of at least 2 Gms. or a total of 3.420 Gm. Instead we get 3.312—or a decrease in the normal flow, plus the added amount.

The administered bile products therefore do not increase the bile corresponding to the amount given. Instead they are *simply excreted*, and do not actually

stimulate secretion, but appear to lessen the normal secretion.

An analysis of the other cases will show similar results.

When we examine the results of researches on the flow of bile we are convinced that all workers have stated their results correctly, but may have drawn erroneous conclusions because they visualized the conditions erroneously.

The results of these experiments force us to the following conclusion.

In the normal animal or man, the secretion of bile, like the secretion of urine is at a maximum for a 24 hour period. No drug, even bile itself will increase the normal 24 hour flow. However if the flow of bile is subnormal, (similarly with the secretion of urine) there are drugs which may increase the flow temporarily. For this reason the results for a shorter period may show the effect of a drug; better than for a 24 hour period.

What we have said does not imply that bile may not have a useful function in therapeutics. If there is an inadequate secretion of bile due to constipation or other causes, bile administration may be helpful. In addition, in surgical cases where an increased flow of bile is desired through the bile ducts, it may serve a useful function. Gauss⁵ has called attention to biliary constipation due to a reduced formation or flow of bile. He has treated hundreds of such cases (personal communication) successfully by using bile salts.

That decrease in bile flow, may cause constipation is supported by the experimental results of Ivy⁶ et al who found that distention of the proximal colon in the dog and monkey inhibits bile flow. We may conclude therefore that in constipation there is a decrease in flow or formation of hepatic bile flow. Also that anything that relieves constipation must influence the flow of bile. Such relief could occur from the use of bile a choleric or a cathartic.

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Evaluation of the Laxative Effect of Some Commonly used Laxative Substances: With Particular Reference to Dosage*

By

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WRONG hygienic habits may lead to constipation. In its early stages, this type of constipation may be remedied by dietetic measures, abdominal massage, suitable exercises, hydrotherapy, regular evacuation time, and similar measures. To some patients, however, these therapeutic measures may appear too formidable and time consuming to use in a relatively benign though uncomfortable condition. The patient's condition may not permit such treatment. Advanced age, chronic cardio-vascular disease or a pulmonary lesion may constitute contraindications to dietetic regulation or physiotherapy. Quite often, the patient with chronic constipation may not find it possible or convenient to

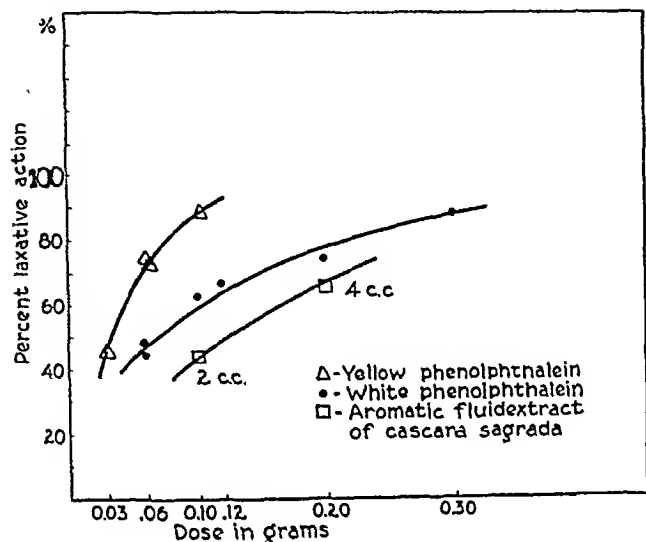
adhere to a prescribed dietetic and hygienic regimen. In such cases, laxatives are not only valuable, but often the only available measure toward the accomplishment of the therapeutic aim. Such patients should be encouraged to obtain daily evacuation by mechanical means. The suggestion that they should be left to go without evacuation for days, since some individuals exhibit no untoward symptoms of their irregularity, appears to us without merit. This viewpoint receives support in Blumer's *Therapeutics*.¹

There is a widespread prejudice against the daily evacuation by use of laxatives. This prejudice is well founded, but, when erected into a principle, is entirely without justification. Self-drugging leads almost inevitably to certain abuses, but the systematic use of drugs under intelligent guidance is objectionable in theory only. People quite correctly object to "becoming enslaved to the use of drugs" but it is hard to choose between the liberal use of certain fruits on the one

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hand and the employment of the active principle of fruits on the other. While it is not ordinarily judicious to advise any young person to adopt the steady use of drugs for the relief of constipation, this advice in preference to any other may often be given to adults.

Notwithstanding the statement of some medical writers that the use of laxatives is a "horrible habit," laxatives have a well-defined place of usefulness in the



Graph 1.

management of chronic as well as in the relief of temporary constipation.² A patient confined to bed by illness can certainly not be expected to submit to a dietetic and physical regimen to overcome his constipation. Under such circumstances, certain drugs have demonstrated their usefulness and have continued to be employed widely, though at times their indiscriminate use may not be advisable. Such drugs are phenolphthalein, senna, aloë, cascara sagrada, rhubarb, podophyllum, and magnesia. Lubricants, such as mineral oil, demulcents ("smoothage" represented by agar and the gums), and roughage (represented by bran), are extensively and effectively used as ant-constipation substances.

The effective dose of these substances in constipation obviously varies with the intensity of the condition. Patients with constipation of shorter duration need less medication, while those with constipation of a chronic nature require more. In prescribing the drug, it is important to give the optimum dose so as to produce the desired laxative effect but without purgation. An inadequate dose will be without effect and may discourage the patient, causing him to turn to self-elected measures often of questionable value. The use of too large a dose will result in a purgative effect associated with possible subjective symptoms such as cramps, flatulence, etc.—and consequent bowel irritation followed by constipation. For continued use a dose that is neither too small nor too large is advisable.

As a rule the dose of any medication should approximate the dose prescribed in the Pharmacopoeia. Even though the officially established doses are often inade-

quate and ineffective, pharmacopoeial doses should be accorded preference in prescribing the greater number of drugs. However, in regard to the laxative drugs certain deviations from this rule appear desirable. While making investigations with laxatives on both normal and constipated individuals we were impressed with the variability of the laxative effect of these substances when used in doses conforming to those prescribed by the Pharmacopoeia XII. Because of this observation, we have undertaken the study which forms the basis for this report.

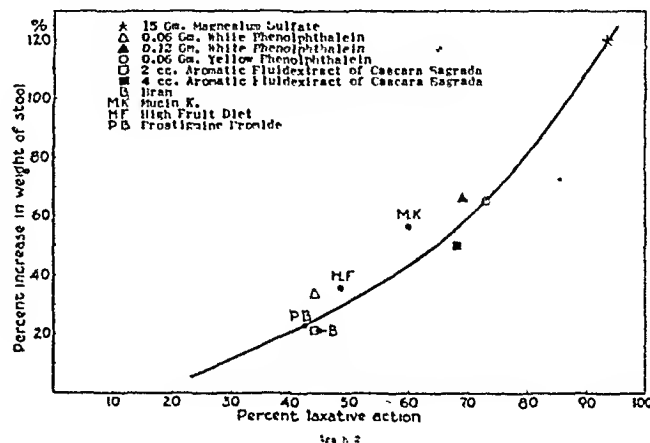
Material and Methods

Normal individuals as well as constipated patients were used in our tests. At certain intervals, each individual was given one of the laxative drugs in a dose closely approximating the Pharmacopoeial dose. The effect on bowel movement, the number and consistency (hard, soft, liquid) of the stool were observed or established in each subject. Whenever possible, the moisture content and the weight of the stool were determined. In some cases the subjective symptoms following the drug were recorded. Because many of our previous investigations were with phenolphthalein, the majority of the observations were made following the administration of phenolphthalein.* For comparison, however, laxative results after cascara, magnesium sulfate, bran, Karaya gum,** and high fruit diet were also studied. In normal subjects, we considered an increase in number and weight of stools and change in consistency as laxative effect. In constipated cases, the occurrence of a bowel movement was an additional sign of laxative effect.

Results

The results are shown in the tables.

A laxative effect was obtained in 48% of normal subjects with the U. S. P. dose (0.06 Gm.) of phenolphthalein; in 63% who received 0.1 Gm., in 74% who received 0.2 Gm., and in 88% who received 0.3 Gm. phenolphthalein.



Graph 2.

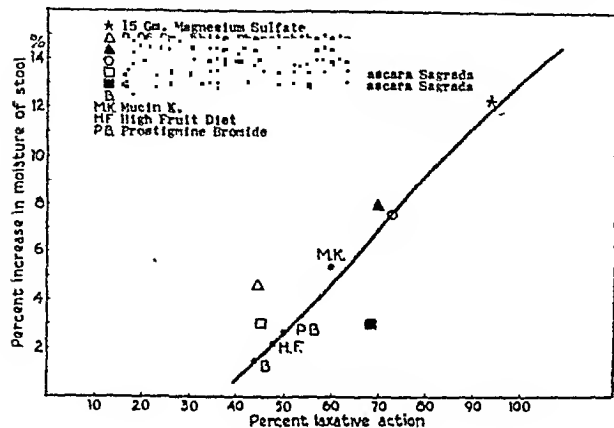
A dose of 0.03 Gm. yellow phenolphthalein produced a laxative effect in 45% of cases, and following a dose

(*) Phenolphthalein or U.S.P. Phenolphthalein is White Phenolphthalein in graphs and tables.

(**) Karaya gum is Mucin-K in graph.

of 0.06 Gm. yellow phenolphthalein 74% had a laxative effect (Table 1).

Another group of normal individuals studied several months later gave quite similar results. Thus, a laxative effect was obtained in 44% of the cases receiving 0.06 Gm. phenolphthalein, in 66% receiving



Graph 3.

0.12 Gm. phenolphthalein and in 73% of 114 individuals receiving 0.06 Gm. yellow phenolphthalein (Table 2).

A group of patients with constipation of recent oc-

yellow phenolphthalein. Following this dose 56% of 16 habitually constipated patients, and 67% of patients with constipation of recent origin had a laxative effect. Following a dose of 0.12 Gm. U. S. P. and 0.12 Gm. yellow phenolphthalein mixed together, a laxative effect was obtained in 75% of 120 habitual and in 86% of 121 individuals who recently became constipated (Table 4).

Since phenolphthalein is but slightly soluble in water, the laxative effect of 0.1 Gm. phenolphthalein in alcoholic elixir was determined in 34 normals and in 171 patients. A laxative effect was obtained in 80% of both groups (Table 5).

Micro-crystalline phenolphthalein*, when given in doses of 0.03 Gm produced a laxative effect in 54% of 28 individuals and, in doses of 0.06 Gm. in 65% of 76 subjects (Table 6).

U. S. P. doses of aromatic fluidextract of cascara sagrada produced laxative effect in only 44% of 10 cases. Twice the U. S. P. dose of aromatic fluidextract of cascara sagrada and U. S. P. doses of magnesium sulfate produced laxative effects in 66% of 21 and 94% of 31 normal subjects respectively (Table 7).

The doses generally recommended of a demulcent substance produced a laxative effect in 60% of 30 individuals. Artificial "roughage" (bran) was effec-

TABLE I

Phenolphthalein Dose and Type	No. of Cases	Percent Laxative Effect	Average No. of Stools		Percent Increase in No. of Stools	Percent of Subject having:			
			Before	After		Change in Consistency	Liquid Stools	Increase in No. of Stools	Cramps
0.06 Gm. U.S.P.	60	48%	1.17	1.40	19.6%	41.6%	16.7%	21.7%	15.0%
0.10 Gm. U.S.P.	86	63	1.40	1.92	37.1	56.8	24.4	40.7	17.4
0.20 Gm. U.S.P.	205	74	1.37	2.00	46.0	64.4	40.0	52.7	27.8
0.30 Gm. U.S.P.	24	87.5	1.38	2.58	87.0	87.5	62.5	75.0	37.5
0.03 Gm. Yellow	51	45	1.27	1.47	15.7	41.2	23.5	27.5	11.7
0.06 Gm. Yellow	124	74	1.35	2.04	51.1	68.5	46.0	47.6	25.0

U.S.P. Phenolphthalein is White Phenolphthalein.

TABLE II

Phenolphthalein Dose and Type	No. Studied	% Laxative Effect	Average Number of Stools		% Increase	Average Weight of Stools in Gms.		% Increase	Average % Moisture Content		% Increase	Flatulence	Cramps
			Before	After		Before	After		Before	After			
0.06 Gm U.S.P.	122	44%	1.03	1.20	16.5%	99	132	33%	73.7	77.1	4.61%	32.7%	19.3%
0.12 Gm U.S.P.	155	66	1.01	1.28	26.7	97	161	66	73.3	79.3	8.15	38.0	30.7
0.06 Gm Yellow	114	73	1.05	1.30	23.8	97	160	65	73.6	79.2	7.63	42.5	37.7

currence had somewhat similar results as those of the normal groups, i.e., a laxative effect was obtained in 44% after a dose of 0.1 Gm. of phenolphthalein, in 75% after a dose of 0.2 Gm. phenolphthalein and in 82% of 34 cases on 0.3 Gm. phenolphthalein.

Of 37 patients receiving 0.1 Gm. yellow phenolphthalein 89% had a laxative effect (Table 3), without complaining of untoward symptoms.

A small group of patients was given a capsule containing a mixture of 0.06 Gm. U. S. P. with 0.06 Gm.

tive in 44% of 50 subjects, and natural roughage (fruit) in 48% of 31 subjects (Table 8)

Discussion

As shown in the tables, the Pharmacopoeial dose of phenolphthalein may not produce a laxative effect. If one accepts a laxative effect in over 50% of the

(*) Microcrystalline phenolphthalein is obtained by the precipitation of phenolphthalein in a colloidal solution, such as Indian gum. This results in a very fine division and crystalline formation and reduces the size of the particles from about 80 microns to about 6 microns.

cases from a certain dose of a drug as the basis for establishing its therapeutic dose, the present Pharmacopoeial dose of 0.06 Gm. phenolphthalein is not large enough since in various groups of subjects it consistently failed to produce laxation in 50% of the cases observed. Only when the dose of phenolphthalein was raised to 0.1 or 0.12 Gm. did a laxative effect occur in over 50% (i.e. 66%) of the normal

years later under different conditions and over a much longer period of time. Nevertheless, the percentage of laxative effect obtained following similar doses of U. S. P. or yellow phenolphthalein as previously used, in the two groups is strikingly close (48%, 63%, 75% as compared to 44%, 66% and 73%).

It is therefore evident that almost twice the Pharmacopoeial dose of phenolphthalein is needed to cause

TABLE III

Type of Laxative and Dose	Number of Subjects	Percent Laxative Effect	Stools per subject following Laxative			
			Subjects Having:			Ave. No. Stools
			None	1	2	
0.100 Gm. U.S.P. Phenolphthalein	41	44%	23	11	7	0.60
0.200 Gm. U.S.P. Phenolphthalein	263	75	64	160	39	0.91
0.300 Gm. U.S.P. Phenolphthalein	34	82	6	23	5	1.00
0.100 Gm. Yellow Phenolphthalein	37	89	4	25	8	1.10

TABLE IV

Type of Patient	Type of Laxative and Dose	Number of Patients	Percent Laxative Effect	Number Stools Following Laxative (per Patient)							Percent Liquid Stools	Average No. of Stools After Dose	Percent Having Cramps
				None	1	2	3	4	5	6			
Chronic	U.S.P. and Yellow Phenolphthalein, of each 0.06 Gm.	16	56.3%	7	5	2	2				0	0.94	11.1%
Recent	"	30	66.7	10	9	9	2				0	1.10	
Chronic	U.S.P. and Yellow Phenolphthalein, of each 0.12 Gm.	120	75.0	30	40	25	16	6	2	1	11.75	1.48	23.76
Recent	"	121	86.0	17	26	38	21	15	3	1	13.40	2.03	

TABLE V

Laxative Effect of 0.100 Gm. U.S.P. Phenolphthalein in Alcoholic Elixir.

	Number of Cases	Percentage			Average No. Stools		Percent Who Had Cramps
		Laxative Effect	Liquid Stools	Increased No. Stools	Before	After	
A. Normals	34	80%	63%	80%	1.4	2.8	42%
B. Hospital Patients	171	80			0	1.6	

TABLE VI

	Number of Cases	Percentage				Average No. Stools		Percent Increase	Percent Cramps
		Laxative Effect	Consistency Change	Liquid Stools	Increase in No.	Before	After		
0.03 Gm. Microcrystalline Phenolphthalein	28	53.6%	46.4%	25.0%	32.1%	1.43	1.64	14.7%	14.3%
0.06 Gm. Microcrystalline Phenolphthalein	76	64.5	61.8	35.5	46.1	1.38	1.92	39.1	21.1

individuals. In constipated cases, the laxative effect passed the 50% mark only after doses of 0.2 Gm., while in some constipated patients, larger doses (0.3 Gm.) were frequently necessary.

The results reported here apply not only to a limited group of individuals but also to a great number of cases observed at various times and under different environmental conditions as is shown in the accompanying tables. The 550 subjects in Table 1 were "normal" individuals of both sexes, tested over a comparatively short period of time, while the 351 subjects in Table 2 cover a more homogenous group of predominantly male students who were tested two

laxative effect in normal individuals. Increasing the dose causes only a gradual rise in the incidence of laxative effect. Thus, the laxative effect of 44% from the 0.06 Gm. dose is increased to only 63% by a 0.12 Gm. dose, and further doubling of the dose increases the percentage only another 11% (Graph 1). As will be shown later, the greater the dose the more likely is the occurrence of some accessory effect, consequently it is well to keep the dose near the established optimum, which in this instance would be between 0.12-0.2 Gm.

Similarly (as in the normal subjects) the two groups of patients although differing in the number of each sex in the group, (the first group had a larger num-

ber of women in it) and not tested simultaneously, showed closely identical laxative percentages following approximately equivalent doses of phenolphthalein. That the percentage of laxative result in patients was in general somewhat lower in both groups of 375 and 287 cases respectively than in the normals receiving similar doses, is easily understandable, as is also the fact that laxative effects were found in higher per-

from patient's remarks (Graph 2 & 3). This fairly close parallelism is due to the fact that patients consider the passage of a voluminous or watery stool as a sign of laxation.

The laxative results were inadequate not only with the Pharmacopoeial dose of phenolphthalein but also with the Pharmacopoeial dose of aromatic fluidextract of cascara sagrada. The Pharmacopoeial dose of mag-

TABLE VII

	Number Cases Studied	Percent Laxative Effect	Average Number of Stools		Percent Increase	Average Weight of Stools in Gms.		Percent Increase	Average % Moisture Content		Percent Increase	Flatulence	Cramp
			Before	After		Before	After		Before	After			
Arom. Fldextr. Cascara Sagrada 2 cc	10	44%	0.94	1.0	6.4%	95	115	21%	75.5	78.4	3.84%	44%	11%
(Ibid) 4 cc.	21	68	0.96	1.25	30.2	91	147	61.5	73.8	76.0	3.0	32	14
Magnesium Sulfate 15 Gm.	31	93.5	0.95	1.48	55.8	92	203	120	74.3	83.5	12.4	55	55

TABLE VIII

Type of Laxative	Number Cases Studied	Percent Laxative Effect	Average Number of Stools		Percent Increase	Average Weight of Stools in Gms.		Percent Increase	Average Percent Moisture Content		Percent Increase	Flatulence	Cramp
			Before	After		Before	After		Before	After			
Karaya Gum	30	60%	0.96	1.18	22.9%	92	144	50%	74.4%	78.4%	5.1%	50%	36.7%
Bran	30	44	1.08	1.13	4.6	100	121	21	74.3	75.5	1.6	12	8.0
High Fruit	31	48	0.95	1.18	20.4	92	125	32.3	74.3	75.9	2.2	32.3	6.5

TABLE IX

Laxative Effect—According to Age Groups

0.100 Gm. White Phenolphthalein in Alcoholic Elixir

Age	Number	Number Having Laxative Effect	Percent Having Laxative Effect	Not Laxative	Percent not Laxative	Number of Stools	
						2+ and More	3+ and More
20—29	24	19	79.2%	5	20.8%	58.3	33.3
30—39	32	27	84.4	5	15.6	40.6	12.5
40—49	27	22	81.5	5	18.5	37.0	25.9
50—59	31	27	87.1	4	12.9	41.9	16.1
60 and over	34	29	85.3	5	14.7	41.2	14.7

centages in the recently than in the habitually constipated cases. All these results, quite similar in the various groups, reemphasize the fact that the present U. S. P. dose of phenolphthalein is inadequate to produce a laxative effect; the laxative effect occurs in constipated individuals only after the dose is at least trebled.

It appears logical to assume that the reason larger doses than 0.06 Gm. of phenolphthalein are necessary to produce a laxative effect is the marked insolubility of this substance. This assumption might be supported by the fact that when 0.10 Gm. phenolphthalein was given dissolved in an alcoholic elixir, an 80% laxative effect was obtained in normal subjects and in patients (Tables 5 and 6).

That the patients' evaluation of the effect is fairly correct can be gleaned from Tables 2, 7 and 8. From these tables it may be seen that the increase in the weight and moisture content of the stool more or less parallels the percentage of laxative effect as gathered

from patient's remarks (Graph 2 & 3). This fairly close parallelism is due to the fact that patients consider the passage of a voluminous or watery stool as a sign of laxation.

Recent investigations dealing with the action of phenolphthalein and its absorption and elimination from the body,³ its customary use and its laxative effect in various doses, point to the fact that the original Pharmacopoeial dose of phenolphthalein of 0.2-0.3 Gm. and the dose of the British Pharmacopoeia (0.06-0.3 Gm.) was more likely the optimum dose than the present day one. It is possible that the dose of 0.2 to 0.3 Gm. of the early Pharmacopoeia may have been excessive for the average person because the early phenolphthalein did not attain the purification of the phenolphthalein of today. It retained more of the yellow bodies which imparted greater laxative efficiency to the drug. This may have resulted in the change of

TABLE X
Laxative Effect—According to Age and Whether
Recently or Chronically Constipated

(Following 0.12 Gm. each Yellow and U.S.P. Phenolphthalein)

(A)

Age	Number and Percentage of Cases in Which Laxative Effect Was Produced					
	Recent		Chronic		Combined	
	Number	Percent	Number	Percent	Number	Percent
20—29	18	77.8%	7	85.7%	25	80%
30—39	25	84.0	7	85.7	32	84.4
40—49	23	82.6	33	79.0	56	80.0
50—59	57	84.2	44	68.2	101	77.3
60 and over	50	88.0	44	68.2	94	78.8

Laxative Effect of Two or More Bowel Movements
—According to Age and Whether Recently or
Chronically Constipated

(Following 0.12 Gm. each Yellow and U.S.P. Phenolphthalein)

(B)

Age	Percent of Cases		
	Recent	Chronic	Combined
20—29	66.7%	71.0%	68.0%
30—39	68.0	57.0	65.6
40—49	47.6	31.0	50.0
50—59	57.9	22.7	42.5
60 and over	46.0	31.8	39.3

Laxative Effect of Three or More Bowel Movements
—According to Age and Whether Recently or
Chronically Constipated

(Following 0.12 Gm. each Yellow and U.S.P. Phenolphthalein)

(C)

Age	Percent of Cases		
	Recent	Chronic	Combined
20—29	22.2%	57%	32%
30—39	32.0	14.0	28.1
40—49	39.0	21.0	28.5
50—59	14.0	13.6	13.8
60 and over	16.0	13.6	14.9

the dose of phenolphthalein to 0.06 Gm. In its present pure form, however, the 0.06 Gm. dose is not a laxative dose. Purification may have failed to attain its aim in the present instance by depriving the drug of its activity rather than enhancing it, without appreciably affecting its negligible toxicity.

In discussing the laxative dose of phenolphthalein it must be mentioned that the extremes of life must be especially considered. We have noted that higher age groups need larger doses (Tables 9 & 10). Similarly, it was found that children up to twelve years of age also need comparatively larger doses than the average adult.⁴

The two most common untoward effects of a laxative drug are cramps and flatulence. The incidence of either may increase with increase in the dose. Hence, too large a dose should be avoided. From the experiences with constipated patients we believe that 0.2 Gm. phenolphthalein represents the optimal dose for laxative and also for minimal side effects.

Summary

Habitual constipation is a common disorder, which, some opinion to the contrary notwithstanding, frequently requires laxative drugs for its most satisfactory treatment.

The effects of some of the most commonly used laxatives are compared.

The U. S. P. dose of phenolphthalein (0.06 Gm.) or of aromatic fluidextract of cascara sagrada (2 cc.) is ineffective. 0.20 Gm. of phenolphthalein and 4 cc. of aromatic fluidextract of cascara sagrada are the optimal doses.

The aged and children require larger doses of phenolphthalein than the average adult.

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This study was started under the direction of the late Dr. B. Fantus. The Misses H. Dyniewicz, Ph.C., E. Redding, R.N., E. Carlson co-operated in these investigations.

Problems of Differential Diagnosis in Diseases of the Gastro-Intestinal and Genito-Urinary Organs

By

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DIAGNOSIS of abdominal diseases is one of the most important problems in medicine. Not only the difficulty of establishing the exact diagnosis, but the decisions following the diagnosis, make this field of abdominal diseases so highly significant. With the diagnosis established, frequently the decision has to be made as to whether we are dealing with a condition of medical character, to be treated conservatively, or whether a more active procedure—surgery—is indicated.

The multitude of organs in the abdominal cavity and the close contact of all these intraperitoneal parts, as well as the common innervation of many of these organs, make it so complicated to establish the correct diagnosis. The very fact that intraperitoneal and extra—or retroperitoneal organs—are in close apposition, and that involvement of organs of both spaces may show similar signs and symptoms, increases the difficulties in establishing the diagnosis in "abdominal" diseases.

Especially, the vicinity of the genito-urinary organs complicates the problem. In a transverse section at any level below the diaphragm we find organs of the intraperitoneal and the retro—or extra peritoneal—spaces in close contact. Pathology of organs of either space may present the signs and symptoms characteristic of those of both the gastro-intestinal and genito-urinary systems.

Whatever clinical symptoms the patient may show often fits into diseases of both systems. Pain, even if localized, may originate from both systems. Pain, if radiating, may aid in establishing the diagnosis as to whether the diseased organ is part of the gastro-intestinal or the genito-urinary tract. But at the same time the presence of radiating pains may make the decision even more complicated.

The highly important and alarming symptoms of sickness and vomiting may be present in diseases of both systems. We know that any disease of the genito-urinary organs may be accompanied by severe sickness and vomiting, just as in primary involvement of the gastro-intestinal organs. Tenderness and rigidity of the abdomen, both characteristic signs of intraperitoneal inflammation, may be found as well in the diseases of genito-urinary organs. Discharge of blood to the outside is mostly attributed without any difficulty to the system from which it originates. Blood from the gastro-intestinal organs which empties through the anus is easily recognized as to its source, while blood found in the urine proves its origin from the urinary system. Only in exceptionally rare cases as, for instance, in infants, there may be doubt as to whether the blood comes from either of the two sys-

tems. In women, the pelvic organs may be another source of diagnostic difficulty.

From the clinical aspect and examination often no decision can be made as to whether the chronic or acute condition in question originates from the gastro-intestinal or genito-urinary organs. The multitude of laboratory and roentgenological methods must be applied to establish a diagnosis and eliminate differential diagnostic difficulties. Furthermore, one of the most important ways of establishing a diagnosis and eliminating differential diagnostic difficulties concerning the system involved is, of course, the cystoscopy. Complete urological check-up includes a thorough examination of the bladder using the cystoscope, functional test of the kidneys by intravenous injection of dye, catheterism of the ureters with the collection of split specimens from both kidneys, as well as retrograde (instrumental) and intravenous pyelography. Very often already the first flat plate of the abdomen establishes the diagnosis as, for example, in the presence of stones somewhere in the urinary system.

Beginning with the kidneys as diagnostic problems in our case, we have to differentiate between two large groups of kidney diseases: stones and tumors. The highly important kidney tuberculosis can be ignored in this paper, hardly ever being a problem as far as we are concerned. On the other hand, stone disease of the kidney, if not complicated by microscopic or macroscopic hematuria may present a most confusing picture. Pain of chronic, intermittent character, or of acute onset, just as in an abdominal catastrophe, may be one of the problems with which we have to deal. Complications, as in primary involvement of gastro-intestinal organs, may confuse the picture of stone disease of the kidney; sickness and vomiting, retention of gas and feces, tenderness and rigidity, as well as distention of the abdomen, may be found in kidney stones as well as in gastro-intestinal diseases. Radiating pain into the bladder region is certainly a very characteristic symptom in the former. But we should not forget that radiating pain may be entirely absent or its direction may point toward intraperitoneal organs thereby complicating the clinical picture. Roentgenological examination, laboratory findings and complete cystoscopy will eliminate these doubts.

Tumors of the kidney, especially the dangerous malign hypernephroma, if accompanied by hematuria, are no differential diagnostic problems in this connection. But if the patient complains only of a mass in the upper abdominal region and a sensation of fullness, with disturbances of gastro-intestinal organs from the tumor pressure, the differential diagnosis stands be-

tween gastro-intestinal obstruction and extra—or retroperitoneal growth. Thorough examination in these doubtful cases mostly starts with roentgenological check-up of the gastro-intestinal tract. If a diagnosis can not be established by these means then complete cystoscopy and roentgenological examination of the urinary tract, as described above, ought to be done.

The problem of hydronephrosis should also be considered under the heading of "tumors". Hydronephroses are tumor masses in the lumbar region. These tumor masses may influence secondarily the intraperitoneal organs, just as in cases of real tumor (growth) of the kidney. All the signs and symptoms of intestinal obstruction may arise: sickness and vomiting, tenderness and rigidity, abdominal distention may complicate a hydronephrotic kidney and present a clinical picture or appearance of primary gastro-intestinal involvement.

Thus a solid tumor (such as hypernephroma) has the same effect as hydronephrotic enlargement of the kidney. Both forms appear as a mass and may influence secondarily the gastro-intestinal tract.

The differential diagnosis—as to whether we have to deal with hydronephrosis or gastro-intestinal pathology—may be established in some cases simply by palpation: the typical balloon-like mass in the kidney region, often extending directly into and toward the intraperitoneal organs, is characteristic of hydronephrosis. In addition, complete cystoscopy will help to clear the picture.

Diseases of the ureter may give rise to the same signs and symptoms as affections of the kidney. Radiating pains either upward into the kidney or down to the bladder and penis and disturbances of micturition in clear cases do not present any difficulty in diagnosis. If, in addition, we have a microscopic or macroscopic hematuria, the clinical diagnosis indicates stones in the ureter. But we should never forget that hematuria may be found also in primary intestinal diseases. Cases with right-sided abdominal pain, without radiation toward the bladder, may show blood in the urine: here we may have to deal with a primary intraperitoneal disease. For appendicitis, mostly of acute, but occasionally also of chronic character may be accompanied by microscopic or macroscopic hematuria. Retro-cecal position of the appendix brings it into direct proximity to the right ureter, running down in the retro-peritoneal space. Chronic adhesions of such a retro-cecal appendix, but more frequently an acute inflammation may cause a ureteritis with hematuria. We should, therefore, never be deceived by the presence of hematuria, because we may fail to establish in time the diagnosis of an acute appendicitis. In cases of abdominal situs inversus viscerum, with left sided pain, the diagnosis of a left sided appendicitis (if complicated by hematuria) is even more difficult—perhaps impossible—to establish. We know that stones in the ureter may frequently be accompanied by disturbances of micturition although even here there may be a problem in differential diagnosis between gastro-intestinal and genito-urinary pathology.

Despite the extra-peritoneal location of the urinary bladder we may find some difficulties in diagnosis. Hematuria in a questionable affection of the lower abdomen in the pubic region indicates the involvement of the urinary tract. The urinary bladder is one of the likely sites of disturbance. However, in chronic or acute cases of abdominal distention with rigidity, tenderness and a tumor-like mass in the lower abdomen, complicated by retention of urine, we must not overlook intraperitoneal causes as well. For once the retention of urine in the bladder may be of primary origin, causing secondarily intraperitoneal disturbances (paralytic ileus): these complications may quickly disappear after catheterism of the bladder. On the other hand, primary intraperitoneal localization which causes intestinal paresis with all the signs and symptoms of a paralytic ileus, may secondarily influence the bladder and its emptying ability. It is understood that catheterism in this case will not improve the patient's condition. Possibly, in such a case of secondary disturbance of the bladder function there may even be a decided absence of urine in the bladder, the intraperitoneal pathology having already caused a renal anuria. Diagnostic steps in these cases should, therefore, emphasize the well-known methods of gastro-intestinal diagnosis (roentgenological G.I. Series, barium enema, etc.)

A special problem in differential diagnosis between gastro-intestinal and genito-urinary tract is presented by all forms of injury. An injury to the region below the diaphragm may result in a lesion to organs of both gastro-intestinal and genito-urinary systems. These cases present very difficult problems, especially since the decision as to whether surgery is indicated or not, has to be made entirely on the quick and exact diagnosis. Depending upon the causing factor the resulting injury may be a perforation by a bullet or a stab wound, a crushing of one or more organs by a heavy blow against the abdominal or lumbar regions, or hematomas from explosions, etc. Intraabdominal ruptures, tears, as well as retro- or extra-peritoneal injuries of kidney, ureter and bladder may result. In doubtful cases of rupture of the bladder catheterism may clear the picture, although it should not be forgotten that a bladder irrigation in such a case may cause further damage by complete severing of the bladder where previously we had only a partial tear.

If the general condition of the patient after an accident allows any diagnostic procedure at all, it is better to establish quickly the exact diagnosis as to the system involved. This, followed by surgical procedure at the right time and the right place, will help more than any "exploratory" operation without exact diagnosis and without localization of the traumatic lesions involved.

Street accidents, injuries in factories, war plants, etc., and especially the numerous wounds resulting from modern warfare, may present problems concerning the exact diagnosis.

Severing of the ureters, a rare occurrence due to the small size of the normal ureter, may occur from bullet and stab wounds. The diagnosis can be obscured by

development of a hematoma in the retro- or intraperitoneal spaces which, by pressure on intraperitoneal organs then presents the picture of a gastro-intestinal lesion. Extravasation of urine from the affected kidney may, at least for the first few hours after the injury, increase the pressure of this tumor-like mass. Combined injuries of the urinary and intraabdominal organs may result in early peritonitis, from lesions in the gastro-intestinal or urinary organs. Such a perforation of organs of both the gastro-intestinal and the urinary systems from a bullet or a stab wound may complicate the diagnosis. Injuries to the urinary bladder may be extra- or intraperitoneal. The urine emptying through the hole in the bladder may enter the soft tissue of the perivesical space, or the intraperitoneal cavity. Real peritonitis may result, or secondary pressure on the intraperitoneal organs from the accumulation of urine in the perivesical space.

Differential diagnostic problems between diseases of the male genital organs and the gastro-intestinal tract are fewer. One important clinical picture, though, may come up in males under the signs and symptoms of a fully developed peritonitis: tenderness and rigidity in either the lower left or right abdominal quadrant, distention, sickness and vomiting may be present. If the right lower quadrant is involved one may be inclined to make the diagnosis of an acute appendicitis.

Nevertheless, all this does not fit into the picture of an acute appendicitis or peritonitis. Blood count, especially white cells, may be normal or only slightly increased—rectal examination, which should never be forgotten in examining abdominal cases, may not reveal any pathology. The entire problem in such a case may be that of a relatively harmless acute deferentitis. There may be no swelling of the scrotal part of the vas deferens at all, but on palpation the finger feels in the inguinal canal the highly painful spermatic cord, causing the secondary, (but harmless) peritoneal reaction. If occurring on the right side it may easily be mistaken for an acute appendicitis. Sometimes it is difficult to differentiate between a hernia and a hydrocele, especially when both are combined and complicated by adhesions from wearing a truss.

It is obvious that many problems can arise from diseases of the female genital organs in differential diagnosis with the gastro-intestinal tract. The discussion of these features, however, would lead this paper too far and it can, of course, cover only a few of the many pictures and problems involved in differential diagnosis between gastro-intestinal and genito-urinary symptoms. It certainly has no ambition of being complete in this respect.

The Role of the Fat Soluble Vitamins A and D in Nutrition*

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MODE OF ABSORPTION OF VITAMIN D AND FACTORS INVOLVED

VITAMIN D can be absorbed from the alimentary tract, and also after intramuscular injection and through the skin. Although the absorption of vitamin D is aided by the presence of fat, this does not apply however to absorption in the presence of mineral oil. Smith and Spector (Smith, M. C. and Spector, H. *Calcium and Phosphorus Metabolism in Rats and Dogs as Influenced by the Ingestion of Mineral Oil*. *J. Nutrition* 20:19, 1940) determined experimentally the effect of the ingestion of mineral oil in puppies on the metabolism of calcium and phosphorus. They noted that the mineral oil interfered with the utilization of vitamin D to such a degree that three times the amount of vitamin D was necessary to cure experimentally produced rickets when mineral oil was included to the extent of five percent of the ration. To such a degree did the mineral oil in the young dog interfere with the retention of calcium and phosphorus that normal calcification did not take place.

Efficient absorption of vitamin D is aided by the presence of bile. This is particularly shown by the fact that vitamin D cannot be properly absorbed from

the alimentary tract when a biliary fistula is established in an animal. However, if the animal is fed taurocholic acid or desoxycholic acid, the absorption of vitamin D is materially aided (Greaves, J. D. and Schmidt, C. L. *The Role Played by Bile in The Absorption of Vitamin D in The Rat*. *J. Biol. Chem.* 102:101, 1933). Obstructive jaundice also interferes with normal absorption of vitamin D.

In this connection, the work of Heymann (Heymann, W. *Metabolism and Mode of Action of Vitamin D*. *Am. J. Dis. Child.* 55:913, 1938) is of considerable interest. Experimenting with rats he ligated the bile ducts. Rickets which had been induced in rats who suffered from the experimentally produced obstructive biliary cirrhosis and jaundice required ten to twelve times as much vitamin D injected intramuscularly as was necessary for the cure of rickets in other rats.

The significance of the intramuscular injection was that it ruled out the possibility of impaired intestinal absorption. Similar results were obtained when the liver was damaged by the administration of carbon tetrachloride. The diminished antirachitic effectiveness of vitamin D was evidently due to the liver disease.

Although the exact mechanism is not clear, the unimpaired liver plays some role in the efficient utilization

* Continued from August issue.

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of vitamin D. When liver disease is suspected, it would therefore be an indication for the administration of more ample dosage of vitamin D.

Because of the disturbance in fat absorption and the loss of calcium salts in the feces in celiac disease, large amounts of vitamin D may be helpful in controlling the disorder.

Absorption of vitamin D occurs mainly from the small intestine. It reaches the blood and then is distributed to meet the needs of the various tissues of the organism. In the normal human being the concentration of vitamin D in the blood is about 50 to 135 International Units in each 100 cc. of serum. In the fish, the liver is a special repository of vitamin D. In the human being however, no such special predilection for the liver is to be found; its distribution is much more general throughout the body wherever there is an accumulation of fat, provided an ample amount of the vitamin is available.

RESULTS OF DEFICIENCY OF VITAMIN D

ONE of the important results of a deficiency of vitamin D, is the development of rickets, a disease bound up with a disturbance of the mineral metabolism, so that normal calcification of bone does not take place. The minerals primarily involved are calcium and phosphorus. In some cases, the concentration of calcium in the blood is normal, but there is a deficiency of phosphorus. In this condition, the ends of the long bones exhibit an overgrowth of cartilaginous tissue of the ribs. Therefore the joints of long bones become enlarged. Along the ribs this increased prominence assumes the appearance of the classical "rachitic rosary." Because of the softness of the bones and their subjection to the weight of the body, the legs become bowed. Confirmatory evidence of the condition is to be found by means of the characteristic roentgen picture of the bones, and also by the demonstration of the low phosphorus determination in the blood serum on chemical examination.

Rickets may also result when the phosphorus in the blood is normal, but there is a deficiency of calcium in the serum. This is often referred to as "low calcium rickets." In this condition tetany may develop, presumably also as a result of low calcium.

Still a third type of rickets has been recognized, due to a deficiency of both the minerals calcium and phosphorus. This is the type known as osteoporosis. The interesting clinical therapeutic fact is that such rickets may be prevented, or in the already established condition, a cure obtained by the administration of vitamin D. The vitamin acts by restoring normal concentrations in the blood of both these minerals, calcium and phosphorus, provided the amount actually present is not too low. Vitamin D accomplishes this remarkable function by increasing the absorption of these essential minerals, from the alimentary tract, and also by preventing undue loss by excretion in the intestine (Sohl, A. T. *Physiology and Pathology of Vitamin D. Chapter XXIV. The Vitamins, 1939, The American Medical Assoc.*)

It is possible that calcium and phosphorus already available and stored in the tissues may be mobilized by means of vitamin D, for deposition in bone and its normal structural development.

While the exact manner in which vitamin D acts to prevent or cure rickets remains an incompletely solved problem (Park, E. A. *The Therapy of Rickets, 115: 370-379, J. A. M. A. 1940*), the important fact remains from a therapeutic point of view, that the vitamin is remarkably effective in the cure of this serious disease. The minerals calcium and phosphorus and vitamin D thus have an important role to fulfill in facilitating normal structural growth and development. The diet should therefore contain a liberal quantity of all three factors. Liberal amounts of vitamin D in the presence of an adequate supply of these minerals will aid in a superior development of the skeletal structure. This is one reason among others why with an improvement in the economic status of people, the children often grow taller than their less fortunate parents reared in early poverty.

In this important field, the fish liver oils have played a prominent role, as readily available sources of natural vitamin D. Coupled with the fact that these oils are also excellent sources of vitamin A, one can readily understand the nutritional value of these commercially available sources of supply. Halibut liver oil, excellent as a source of vitamin A, also contains important quantities of vitamin D, and it therefore ranks among the superior substances in the promotion of skeletal growth. *The Interrelationship of Vitamin D and Calcium and Phosphorus*

However effective vitamin D undoubtedly has proven to be for the development of sound bony structure, one must never lose sight of the fact that the optimum usefulness of the substance is obtained in the presence of a liberal supply of both calcium and phosphorus, the prompt and best utilization of which takes place in the presence of this vitamin.

Osborne and Mendel (*Osborne, T. B. and Mendel, L. B. The Inorganic Elements in Nutrition. J. Biol. Chem. 34:131, Apr., 1918*) in 1918 showed the importance of calcium and phosphorus in the growth of bone. Although growth continued in spite of low levels of sodium, potassium, magnesium or chlorine, such growth was arrested when there was a diminished intake of calcium or phosphorus.

The relationship of the calcium phosphorus metabolism to disturbances of bony structure and the development of rickets was shown by Howland and Kramer (*Howland, J. and Kramer, B. Calcium and Phosphorus In The Serum In Relation to Rickets. Am. J. Dis. Child. 22:105, 1921*). They found the concentration of calcium in normal infants and young children to be from ten to eleven mg. per hundred cc. of serum. Examination made during active rickets showed the calcium concentration to be normal or slightly reduced. A definite reduction in the inorganic phosphorus of the serum always took place in active rickets.

This important interrelationship of antirachitic vitamin to the minerals calcium and phosphorus was also demonstrated by the following contributions. Sher-

man and Pappenheimer (*Sherman, H. C. and Pappenheimer, A. M. A Dietetic Production of Rickets in Rats and Its Prevention by An Inorganic Salt. Proc. Soc. Exptl. Biol. Med., 18:193, 1920-1921*) showed the importance of the addition of potassium phosphate to the diet of rats in the prevention of rickets. The work indicated the importance of the mineral constituents of the diet as well as the fat soluble vitamin factor in the prevention of rickets.

Similarly Mellanby in 1925 (*Mellanby, E. The Effect of Cereals and Their Interaction with Other Factors of Diet and Environment in Producing Rickets. Medical Research Council, Special Report Series (London) No. 193, 1925*) showed the importance of an ample amount of calcium and phosphorus and fat soluble vitamin in the diet for the prevention of rickets in puppies. The causes of defective calcification of bone were found to be due to a deficiency of calcium and phosphorus in the diet as well as of the fat containing the antirachitic vitamin.

Sohl and his associates (*Sohl, A. T., Brown, H. B., Chapman, E. E., Rose, C. S. and Saurwein, E. M.: The Evaluation of the Phosphorus Deficiency of the Rickets-Producing Diet. J. Nutrition 6:271, May, 1933*) showed how restrictions in the amount of phosphorus could seriously limit growth even in the presence of liberal amounts of vitamin D. Growth was retarded when the level of phosphorus in the diet was low, even though the amount of calcium was high and ample amounts of vitamin A and D were administered. This work indicated the importance of phosphorus as well as calcium and vitamin D as factors essential for normal growth. The development or cure of rickets therefore depends on the role not only of vitamin D but of proper amounts of the minerals, calcium and phosphorus as well.

The essential function of vitamin D is to make the blood serum values of calcium and phosphorus normal by increasing the absorption of these minerals from the alimentary tract or by diminishing their loss through excretion by way of the alimentary tract.

In addition to the effect of vitamin D deficiency on the skeletal structures, the various other tissues of the body also suffer, leading particularly to weak and flabby musculature.

The presence of vitamin D deficiency when it has led to actual bone changes may of course be recognized by radiologic examination. This, however, represents an advanced stage of the disorder. Of greater importance are methods of recognition in the subclinical stage, before organic changes in the bony structure

have actually developed. This stage may be suggested by a determination of the concentration of calcium and phosphorus in the blood. Thus the normal value for phosphorus is 4-6 mg. percent and that of calcium is 9-11 mg. percent. A diminution in these values may be an early evidence of subclinical deficiency of vitamin D.

Vitamin D Deficiency and Dental Caries

Mellanby showed (*The Committee for Investigation of Dental Disease. The Influence of Diet on Caries in Children's Teeth (Final Report), Medical Research Council, Special Report Series, No. 211, London, His Majesty's Stationery Office, 1936*) the importance of supplementary additions of fish liver oil in the prevention of dental cavities and the arrest in the progress of dental caries.

In this report Mellanby found "that a relatively high vitamin D content of the food can do much to diminish the incidence of caries if the vitamin is given during the development of the teeth; that a beneficial effect may be obtained if the vitamin is given at a fairly late stage of development, and that when it is given after the eruption of the teeth, the onset and spread of caries is delayed."

Mellanby administered from 700 to 1500 units of vitamin per day, McBeath had also shown the value of vitamin D in favorably influencing the condition of the teeth (*McBeath, E. C. Nutritional Control of Dental Caries. N. Y. State J. Med. 33:1086, Sept. 15, 1933*). In another study McBeath and Zucker (*McBeath, E. C. and Zucker, T. F.: The Role of Vitamin D in the Control of Dental Caries in Children, J. Nutrition 15:547, June, 1938*) recommended the addition of three teaspoonfuls of fish liver oil in the prevention of dental caries.

They reported their observations on the effect of vitamin D on the structure of the teeth over a period of four years on a group of 800 children. The children chosen for this study were from orphanages in and near N. Y. City. The findings of Mellanby were verified as to the effect of vitamin D on dental caries. Their observations led them to the conclusion that vitamin D as well as calcium and phosphorus played a specific role in the normal growth of the teeth and the prevention of caries.

During the period of the year when caries was most common, only the daily administration of 800 units of vitamin D was capable of preventing an increase in the disorder.

(To Be Continued)

Long Standing Fever Due to Regional Ileo-Colitis

By

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IT is the purpose of this communication to report a case of regional ileo-colitis in which the diagnosis was obscured by an elevation of temperature which persisted for several months before the usual clinical and laboratory signs appeared.

Since the increased interest in this disorder occasioned by the publication of the Studies of Crohn and his associates, (1) numerous articles have appeared in the literature. A careful study of those available has brought to light the fact that persistent fever by itself is not a common or outstanding finding in most cases of this disease.

The case report to be presented is that of A.B., 15 years of age, a high school girl of Anglo-Saxon parentage who was first seen by one of us February 15, 1942 complaining of an inflammatory process in the right knee of a week's duration. A tentative diagnosis of acute rheumatism was made and the patient was sent home on salicylate medication along with rest and local heat. She improved rather rapidly and by February 23, 1942 her condition was considered very satisfactory.

About April 15, 1942 she came down with what appeared to be a polyarticular type of rheumatism and after a period of 6 weeks of treatment at her home she was admitted to the Royal Alexandra Hospital. Here she was found to have a sedimentation rate of 30 mm. in one hour (Cutler). During this time her leucocyte count varied from 6,350 up to 9,450 with a normal differential count. She had a moderate secondary anemia. The hemoglobin was 70% (Sahli) erythrocytes 3,550,000. Repeated urinalyses were essentially negative. The Kahn reaction was negative. An electrocardiogram showed a sinus tachycardia of 122, the P. R. interval was 0.16. Physical examination did not reveal any cardiac enlargement nor were there any murmurs heard. There was no clinical enlargement of the liver or spleen and no tenderness elicited on further palpation of the abdomen. Repeated mantoux tests were negative. During the time of her stay in hospital she complained of shifting pains in her joints, her knees particularly being affected. She had a temperature elevation every day varying from 100° to 104°F. In spite of this she did not appear to be quite as ill as would be expected. She exhibited a moderate degree of listlessness and anorexia. As a result further studies were made. Blood cultures were negative, agglutination tests for typhoid, para typhoid A, and B, undulant fever and tularemia were all negative. A chest x-ray was normal in all respects. During this period of observation she had no diarrhoea or

constipation and no abdominal distress. Two transfusions of blood, totalling 500 cc. were administered. After four weeks' observation it was decided to permit her to return home to stay in bed and wait for further developments. Her mother kept a careful record of her temperature but no improvement was noted. Her general condition during her stay at home did not deteriorate appreciably, however, on Sept. 8th after a little over two months of rest at home, she was admitted to hospital once more for a further series of tests. Her first urinalysis showed the presence of a few motile bacilli but a subsequent catheterized specimen was negative in this regard. No significant change was noted in her blood counts. A recheck on the agglutination tests for typhoid, para typhoid, undulant fever and tularemia was negative. Her sedimentation rate remained increased at 23 mm. in 1 hour (Cutler method). The mantoux test was repeated twice with negative results. An x-ray examination of her chest was reported as being negative. In the face of all these negative findings and the fact that her general condition was reasonably good she was once more sent home to await further developments.

The patient was readmitted to hospital October 19, 1942 for a further period of observation. On this occasion it was noted that the patient was tender on deep palpation to the right of the umbilicus. She was apparently unaware of pain in this region and had no particular bowel symptoms such as diarrhoea or other abnormal manifestations.

In view of this, finding an x-ray of the colon was taken. During the course of examination the roentgenologist also remarked about the tenderness elicited by palpation over the right side of the abdomen, however, he was unable to demonstrate any lesion of the colon or terminal ileum. An intravenous urogram was also made and reported negative.

November 1, 1942, she was readmitted to hospital with the same type of fever. On this admission she volunteered the information that her right side was somewhat tender to pressure at times and on deep palpation increased sensitivity was noted for the first time. The possibility of a peri-nephritic abscess was entertained, but x-rays visualizing the psoas muscle revealed no abnormality. An exploratory operation was considered but after consultation with the surgical staff it was felt that the findings were too indefinite and vague to warrant a surgical procedure.

November 7, 1942 a large peri-anal abscess formed and this was incised and drained by one of us, W. S. A. Following this, her temperature subsided completely and immediately she began to notice definite improve-

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ment. On December 13, 1942 she was discharged from the hospital afebrile, with no evidence of a persisting fistula-in-ano.

December 28, 1942 she was once more admitted to hospital with another more deep seated peri-rectal abscess, which drained spontaneously. The only treatment carried out on this visit was the application of hot compresses locally. Surgery was advised but the patient wished to return home until after the holiday season. She was only in hospital three days, during which she had an intermittent fever ranging as high as 100.2°F.

The patient was readmitted to the hospital once more March 3, 1943 with the same type of fever. The patient complained of pain in the rectal region and felt she was going to develop another abscess.

The persistent recurrence of peri-rectal inflammatory changes suggested the possibility of a source higher up. It was noted in a statement by Crohn (1) that many cases of regional enteritis are complicated by fistula formation. A Barium enema was again carried out, in spite of the fact that she never had any definite bowel symptoms. The x-ray findings reported by Dr. A. D. Irvine were as follows: "Radiographically the appearance is that of an inflammatory infiltration in the terminal ileum cecum and lower ascending colon associated with spasm which presents the radiographical appearance of tuberculous ileitis and colitis."

It was felt that clinically this case was more likely to be a regional ileo-colitis than tuberculous disease of the bowel. In view of these findings an operation was advised and one of us, W.S.A., carried out an exploratory procedure which revealed the presence of an inflammatory induration of the lower 3 inches of the ileum and cecum and lower 7 inches of the ascending colon, associated with enlarged mesenteric nodes. A careful search of the rest of the small bowel revealed no skip areas. After a resection of the diseased bowel and lymph nodes was carried out a side to side ileo transverse colostomy was performed. The pathological report made by Dr. M. E. Hall was as follows: "Specimen fixed in formalin of upper colon and distal ileum shows about 6 inches of colon and 3 inches of ileum with a chronic polypoid ulcerative lesion. The bowel wall is thick and rigid and there is definite narrowing of the lumen. Sections show wide areas of both portions of intestine free from mucosa and replaced by chronic granulation tissue in places piled up with a polypoid character. Scattered through granulation tissue are frequent foreign body giant cells—chronic ulcerative and polypoid ileo-colitis, Crohn's disease."

A careful follow up study has been carried out on this patient and up to date no further bouts of fever or peri-anal infection has been noted. Also, the fistula-in-ano has healed spontaneously.

DISCUSSION

Nearly every aspect of regional ileo-colitis has been covered in numerous publications, however, this case seemed worthy of a report because of its atypical manifestation, namely a fever of long standing without any other identifying symptomatology. The term pyrexia of unknown origin which was so popular during and after the last war has been restricted to an ever decreasing number of ailments. This case would suggest that in the differential diagnosis of obscure fevers regional ileo-colitis should be considered. Fever is mentioned in several of the cases reported but it was usually in association with the other typical findings such as abdominal pain, intermittent attacks of diarrhoea and loss of weight.

Hurst (3) was of the opinion that a persistent fever was more indicative of a tuberculous lesion of the bowel and in ileo-colitis fever was present only during the bouts of activity of the disease.

The other outstanding feature of this case was the development of the recurring peri-anal abscesses without other obvious cause. Weisel, Wakefield and Smith (4) reported a study of 12 cases of indeterminate pyrexia which was caused by peri-rectal abscesses. For a time it was thought that this was the explanation in this case as the fever did subside somewhat after incision and drainage was instituted. However, the fact that the abscesses continued to recur seemed to indicate some deeper source.

It should be emphasized that a fairly high percentage of cases of regional ileo-colitis are complicated by peri-rectal or peri-anal abscesses resulting from infections tracking down through the pelvic tissues. It was this observation that finally pointed to the proper diagnosis.

SUMMARY

A case of regional ileo-colitis is presented in which the diagnosis was obscured by a long standing fever for several months before other signs appeared.

The need for considering the possibility of this disorder in the differential diagnosis of indeterminate fevers.

Emphasis is placed on the possibility of peri-anal or rectal abscesses being a presenting symptom of this disorder.

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DR. ELMER HUPPERT

Obituary

Dr. Elmer I. Huppert, chief of proctology of New York University Medical School and assistant attending surgeon of Bellevue Hospital, third division, died recently in Doctors Hospital at the age of 65, after a brief illness.

Dr. Huppert, who resided with his sister, Mrs. Lazarns Rosenberg, at 88 Rugby Road, Brooklyn, was stricken two weeks ago, while on vacation in Florida, and was brought home and admitted to the hospital.

Born in New York, Dr. Huppert was graduated from New York Medical School in 1903 and became associated with Bellevue in 1914, where he has been an

outstanding figure in the field of proctology. He was a consultant at St. John's, Long Beach, Lutheran and Wickersham Hospitals.

Dr. Huppert, who founded the New York Proctological Society, was a fellow of the American College of Surgeons and a member of the New York County Medical Society and the New York State Medical Association group. He was a past president of the New York Society and belonged to Perfect Ashlar Lodge of the Masonic Order. He was also founder of the Green Mountain Boys Camp at Brandon, Vt.

Also surviving are two other sisters, Mrs. Rose Roland and Miss Betty Huppert, and a son, Elmer I. Huppert, Jr.

DR. CHARLES L. GLAESSNER

Obituary

Dr. Charles L. Glaessner was born in Prague, Czechoslovakia in 1876. He received his early schooling and his medical education in the city of his birth. In 1900, he graduated from the medical school of the University of Prague. In the five years that followed, he served as assistant in medicine in various European medical centres, including Strassburg, Wuerzburg and Berlin. During this period, he was actively engaged in post-graduate studies and in research work, chiefly in physiology and physiologic chemistry under the stimulating influence and guidance of some of the outstanding figures of that period: Hofmeister, Ewald and Kraus. Here the groundwork for his contributions to internal medicine were laid. All of his later work bears the impress of these early formative years in experimental medicine. These years produced no less than seventeen contributions many of them dealing with the physiology of digestion: pepsin, rennin, pancreatic enzymes, gastric motility, etc.

In 1905, Glaessner was appointed assistant in internal medicine at the Rudolf Hospital in Vienna. The Viennese atmosphere, medical and social, and the opportunities for work were all to his liking. Here he remained, and here he engaged in active practice, fulfilling with distinction, successively more important hospital and teaching positions, and always at work on some scientific contribution to medicine. In 1909 he was appointed "docent" (associate) in internal medicine at the University of Vienna and in that same year he became chief of the gastro-enterological division of the Allgemeinen Krankenhaus. Then came World War I and active service in the army. Dr. Glaessner served as consulting physician to the armies in Italy and Russia. He was also chief of the epidemic hospitals. For meritorious services rendered during 1914-1918, he was awarded the Franz Josef Order.

Following the war, he was for a brief period, chief of the Malaria Hospital. Then came an uninterrupted period, extending over almost two decades, as chief and director of medicine at the Rainer Hospital (1920-1937) and the Franz Joseph Hospital (1937-1938).

In 1923 he was appointed Professor of Internal Medicine at the University of Vienna. He was a favorite with the student body and popular with the other members of the faculty. As a teacher for the American Medical Association of Vienna he learned to know many Americans who came to Vienna for post-graduate work in gastro-enterology. Some of these have since achieved fame in their own right. These were active, happy and fruitful years. Of the one hundred sixty-three original articles which he contributed to medical literature, almost one hundred appeared during this period, many of them in the Wiener Klinische Wochenschrift and the Archiv fuer Verdauungskrankheiten. His contributions dealt with various phases of internal medicine: they display the originality of thought, the diligent and painstaking care of the true scientific worker. Glaessner's most numerous and most important contributions were in the field of gastro-enterology. During his long career, he enriched the literature with his work on the physiology, chemistry and pathology of the stomach, duodenum, pancreas, liver and gall-bladder; he studied the various ferments, the bile salts, the subject of diet and the metabolism of sugar; he introduced the use of mineral-free water in the treatment of gallstones and kidney-stones and this therapeutic procedure had many followers on the continent where his work was better known. In his monograph, "Ulcus Duodeni" he summed up the then existing knowledge and his own contributions to the subject. He described the ulcer tongue. He also discovered the selective action of the secreting cells of the stomach on neutral red and thereby was able to introduce it into gastro-enterology as an additional test for the study of gastric function. In 1929, his monograph on diseases of the liver and gall-bladder appeared. The amino-acid liver-function test he introduced, served as a basis for many liver-function tests that followed.

Probably nearest to his heart, was his work with pepsin in the treatment of the gastro-duodenal ulcer. His first publication on this subject dates back to 1927. In the years that followed, more than a dozen of his

articles were devoted to the study of this form of treatment and to reports on the excellence of the results. His last efforts before his untimely death were bent upon establishing this mode of therapy in this country.

His work earned for him the respect of his colleagues, just as his warm human understanding and his wonderful sense of humor earned him the love, the admiration, and the devotion of his family, his colleagues and his patients. Many honors were conferred upon him and these he carried with the dignity befitting the man. He was an Officer of the Legion of Honor of France. His own country conferred upon him its highest honor, Hofrat (Aulic Counsellor). He was an honorary member of the Society of Gastro-enterology in Brussels, a corresponding member of the Society of Gastro-enterology in Paris, an Honorary Member of the Royal Society of Medicine (Ghent, Belgium), and foreign collaborator of the Review of Gastro-enterology (New York). He was also a founder of the Union Therapeutic in Paris.

Unfortunately, the upheaval in Europe forced him to leave Vienna in 1938 and after a brief stay in Bel-

gium, he found a haven in this country. He was happy to be here, to get the opportunity to devote himself again to practice and to investigative work. In the four short years given to him, he picked up the threads anew, formed new and respected associations, renewed old ones made at gastro-enterologic congresses abroad and engaged in work in the clinic, and hospitals of New York City. He was associate visiting physician at the City Hospital, lecturer at the Polyclinic Hospital and shortly before his death, was honored by the Fifth Avenue and Flower Hospitals and New York Medical College with an appointment as Associate Clinical Professor of Medicine.

While thus actively at work Dr. Glaessner was suddenly stricken with coronary thrombosis and after a brief illness died on February 26, 1944. Gastro-enterology has lost one of its foremost figures, a man of unusual scientific attainments and an important contributor for forty-five years.

Frank S. Pierson, M.D.

Ernst Hammerschlag, M.D.

Book Reviews

The Standardization of Volumetric Solution. By R. B. Bradstreet. 2nd Edit., Pp. 151. (\$3.75). Brooklyn, N. Y., Chemical Publishing Co., 1944.

As pointed out in the Foreword, a standardized solution is a means to an end and not the end itself. In this book the author attempts to describe in a concise manner methods of standardizing solutions so that they may be used rapidly and without taking time out to look up specific directions in some text or journal. This little volume is frankly meant as "a handy reference work for the man who must hurry to get his results."

While not meant for the beginner, the general principles underlying the methods are usually described sufficiently clearly to make the book useful even to the beginner. Methods used in calibration of volumetric apparatus, preparation of standard substances, preparation of standard solutions of precipitating agents and preparation of standard solutions of oxidizing agents are given. The chapters on indicators and standard solutions of acids and bases should be of interest to the gastroenterologist. Determinations such as those of the acid concentration of gastric contents or the alkali reserve of intestinal contents are essentially based on color changes produced by a given indicator on titrating the sample with alkali or acid. While these chapters are not concerned with titrations of biological fluids, the essential principles involved in these procedures are well presented. Various tables of practical importance in the chemistry laboratory are included. The book is concisely written and is well recommended for the purpose for which it is intended.

Semimicro and Macro Organic Chemistry. By Nicholas D. Cheronis. Pp. 388 (\$2.75). New York, Thomas Y. Crowell Co., 1943.

This is a laboratory manual designed to acquaint the student with the properties of representative organic compounds and with the methods of organic analyses. Unlike numerous other laboratory manuals covering the same field this book presents numerous experiments involving semimicro technic. This is probably a desirable step since in actual practice the student may be faced with testing small quantities of a substance rather than the relatively unlimited amounts to which the more traditional macro methods accustom him. However, not to make the transition too abrupt and for the purpose of contrast, both semimicro and macro methods are included in parallel.

In addition to the 370 pages of text proper and 18 pages of index, numerous questions about each of 70 types of experiments and a number of laboratory report sheets are included as a detachable appendix.

Meant primarily for the student of elementary organic chemistry, the book would appear to fill certain needs in the field of laboratory instruction. For those who are already acquainted with organic chemistry, the description of some of the newer semimicro techniques may be of interest.

The Canned Food Reference Manual. Edited by R. W. Pilcher, 2nd Edition, Pp. 552. New York, American Can Company, 1943.

First published in 1939, this manual has had a wide appeal to those who for reasons of their profession or

business are interested in canned foods. Altho published by a firm whose main business is the manufacture of cans, the book is not a brief extolling the virtues of canned foods and products. It is a factual and authoritative presentation of much material of great importance. Our present-day knowledge of human nutrition is discussed extensively and much information about human mineral and vitamin requirements, the chemistry and methods of assay of vitamins, and the units and standards of vitamins are given. Dietary inadequacies and recommended practices to overcome these deficiencies are discussed. The role of commer-

cially canned foods in maintenance of nutritional balance are of course presented. Useful information on public health aspects of canned foods and on regulations and laws concerned with processed packaged foods are given. The important food, drug and cosmetic act of 1938 is given, and incidentally should be read by all physicians interested in public health and nutrition. A series of 52 tables covering 220 pages, (the caloric values of different foods, the composition of numerous canned foods, the diabetic classification of foods, weight-height relations, etc.) and a selected bibliography complete the volume.

Abstracts of Current Literature

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CLINICAL MEDICINE

STOMACH

THORSTAD, M. J.: *The outlook on carcinoma of the stomach.* (*Am. J. Surgery*, V. 44, P. 242, May, 1944).

Although impressive reports on the treatment of carcinoma of the stomach emanate from large clinics, a truer picture comes from statistics of unselected cases. In Harper Hospital, Detroit, from 1928 to 1942, 454 patients were treated for carcinoma of the stomach. The mortality rate of their operable patients during hospitalization was 26.5 per cent. Thus one-fourth of the patients were in critical condition upon admission. Of biopsies taken, the most common diagnosis was adenocarcinoma. The mortality rate for gastrectomy was 64.7 per cent, but the last twenty such operations (1941-'42) carried only a 29.0 per cent mortality and the number of these operations is increasing. One-fourth of the patients with gastric carcinoma had a normal blood picture. Of 516 patients admitted to Receiving Hospital, Detroit, with carcinoma of stomach 76.6 per cent were clinically inoperable and the hospital mortality rate was 48.1 per cent. While there is no marked annual increase in admissions for carcinoma of the stomach, there has been no marked improvement in the early diagnosis either.—Wm. D. Beamer.

RENSHAW, R. J. F.: *Correlation of roentgenologic and gastroscopic examinations: from the standpoint of the gastroenterologist.* (*Am. J. Roentgen. Rad. Ther.*, V. 51, P. 585, May, 1944).

The comparative value of gastroscopic to roentgenologic examination is rated as being of primary or secondary value. It is of primary value when the diag-

nosis cannot be made by X-ray such as in chronic gastritis and also when gastric ulcers are seen on gastroscopy, but not otherwise. In 150 of a total of 842 patients or 17.7 per cent examined by both methods, gastroscopy was the only means of establishing the diagnosis. Most of these were cases of chronic gastritis but 10 were gastric ulcers. In 55.4 per cent, gastroscopy was only confirmatory, that is, of secondary value especially in the diagnosis of normal stomach. But it also gave more detail as in gastritis in association with an X-ray diagnosed duodenal ulcer etc. If it made the diagnosis definite, for example the malignant or benign nature of an abnormal X-ray shadow, it was considered of primary value also, so that the entire percentage of gastroscopic examinations of primary value was 25.6 per cent. It was of no value in 19 per cent, due to anatomical difficulties mostly, but also to inadaptability on the part of the patient. It is emphasized that gastroscopic examinations should be repeated at least as often as are roentgen studies.—Wm. D. Beamer.

BOWEL

PATTER, E. K. F., AND DOCTER, J. M.: *Carcinoid tumor of the cecum with metastasis.* (*Am. J. Path.*, V. 20, P. 143, Jan., 1944)

The authors present a brief review of the carcinoid tumors of the gastrointestinal tract and list the commoner sites of their occurrence. Carcinoid tumors are rarely encountered in the cecum. Carcinoids have a uniform structure resembling carcinomas. They are usually small and benign and often produce no symptoms. However, the fact that, at times, metastases do

occur points to the potential malignant character of the tumors. They may perhaps be considered as slowly growing malignant tumors. The authors therefore suggest the term "carcinoma of the carcinoid type" to be substituted for the term "carcinoid."

The present report of a case includes a brief history, the patient's course in the hospital and the gross and microscopic autopsy findings.—C. Foderaro.

FELSEN, J. AND WOLARSKY, W.: *Primary intrapapillary adenocarcinoma of the duodenum.* (*Arch. Path.*, 36, P. 428, 1943).

Primary intrapapillary adenocarcinoma of the duodenum is rare, the present case being the 47th to be reported. In this patient the tumor was found to occur at the duodeno-jejunal junction. Clinical signs and symptoms were absent. Adenomatous polyps, submucosal lipoma and two ulcers of the duodenum were co-existent. The authors believe that intestinal pathology is nearly always multiple, as in this case. Diagnosis may be established by means of roentgenographic study of mucosal defects following barium and insufflation with air.—D. A. Wocker.

BRINDLEY, G. V.: *Acute obstruction of the colon.* (*Surg. & Gynec. Obstet.*, V, 78, P. 556, May, 1944.)

In this editorial the writer states that about 20 per cent of the patients with acute obstruction of the colon lose their lives. Carcinoma produces obstruction of the colon in about 80 per cent of the cases, and about 10 per cent of all malignant colon lesions produce obstruction, mostly in the left half. Cancer of the colon occurs chiefly in elderly persons; seventy per cent of the cases being over fifty years of age. This should be borne in mind when the patient is in the older age group and presents symptoms of obstruction of the colon.

The occlusion appears to develop more slowly in the colon than in the small intestine. However, once the blood supply to the involved region is impaired then the change to a serious condition is rapid and may become hopeless in a matter of hours. The biochemical changes noted in small intestine obstruction are absent in colon obstruction.

Treatment is guided by the nature of the pathology. A number of procedures for the various pathologies encountered are outlined. Because most obstructions are due to cancer, wide resection is desirable. However, it should be borne in mind that the patient at this time suffers not only from the malignant lesion but also from pathological changes due to the obstruction. Resection should be done only sometime after a decompression aimed to first protect the viability of the intestine and to restore its normal blood supply.—F. X. Chockley.

GERENDASY, J.: *The importance of proctologic examinations.* (*J. Med. Soc. New Jersey*, V, 41, P. 183, May, 1944.)

While 90 per cent of the ano-rectal lesions we located in areas where they can be either easily palpated or seen by the examining physician, the diseases of the terminal bowel are still unexplored. Nineteen common

diagnostic entities are listed and discussed giving the objective diagnostic features of each.—Win. D. Beam-er.

HILLER, G. I. AND JOHNSON, R. M.: *Abdominal aortic aneurysm. Rupture into the jejunum preceded by occult blood in the stool.* (*Am. J. Med. Sci.*, V, 207, P. 600, May, 1944.)

The authors comment on the rarity of the condition and present the case history and autopsy findings of a 76 year old male. These included an old ulcerated base in the abdominal aorta partly covered by a large thrombus. The base was dilated and formed an aneurysm which had ruptured. A perforation was found in the jejunum and a direct communication between the jejunal perforation and the ruptured aneurysm could be demonstrated.

The authors point to the value of fluoroscopic examinations of the upper G. I. tract to reveal a pulsating mass. Roentgenologic examinations may reveal erosions of vertebral bodies. Pyelography, barium enemas, and especially the presence of occult or gross blood in the stools in the absence of any demonstrable cause aid in the diagnosis of the cases. Apparently an aneurysm of the abdominal aorta is a rare cause of blood in the stools.—C. Foderaro.

PANCREAS

SNELLING, C. E.: *Cystic fibrosis of the pancreas.* (*Arch. Dis. Childhood*, 17: 220, 1942.)

Eleven cases were observed by the authors in 1½ years. It is a pathological entity diagnosed definitely only after microscopic examination of the pancreas. Other fairly constantly associated conditions were bronchiectasis, lung abscess, metaplasia of epithelium and fatty liver. The age incidence was predominantly in the first few months of life. The symptoms were of two groups, nutritional and respiratory. The symptoms referable to nutrition were failure to gain or loss of weight, vomiting, loose and frequent stools, colic and abdominal distention. In some patients symptoms were present from birth. Respiratory symptoms were cough, wheezing, rapid breathing and cyanosis. Malnutrition was present in all. Many showed abdominal distention, hepatic enlargement and 13 were more than 40 percent below normal weight. Physical signs of lung involvement were present in all patients, including bronchitis, collapse and consolidation of the lung, bronchopneumonia and bronchiectasis. The pulmonary infection progressed in spite of chemotherapy and was usually a terminal infection. *Staphylococcus aureus* was isolated from the lungs of all but one patient. Post-mortem examination revealed extensive changes in the pancreas and lungs; the pancreas showing marked and extensive fibrosis; the lung showing plugging of numerous bronchi and bronchioles with thick purulent exudate. It is suggested that lack of vitamin A in the mother may be a probable etiologic factor resulting in her inability to pass this vitamin on to the fetus, or that the condition is primarily in the pancreas as an inherited, congenital or acquired defect.—Courtesy Biological Abstracts.

LIVER AND GALLBLADDER

KARLINSKAIA, A. F.: *Cholecystitis in children.* (*Pediatrics*, 1, P. 26, 1943.)

In 774 autopsies performed in the Rusakov Hospital in Moscow on children from 14 days to 2 years old, 31 cases of undiagnosed cholecystitis were found. Among these were 17 cases of dysentery, 5 cases of toxic dyspepsia, 4 cases of measles, 3 cases of septicemia, 1 case of purulent meningitis and 1 case of diphtheria. Besides these, 1 case of gall bladder hydrops and 2 cases of cholelithiasis were found. The pathological and microscopical findings are described and discussed.—Courtesy Biological Abstracts.

SALMON, G. W. AND RICHMAN, E. E.: *Liver function in new-born infant.* (*J. Pediat.*, V. 23, P. 522, Nov. 1943.)

An attempt is made to estimate the status of hepatic function during the neonatal period as indicated by accepted liver function tests: namely, bromsulfalein excretion and cephalin cholesterol flocculation. Likewise an explanation is sought for the high icterus found in the newborn.

On 79 determinations for packed cell volume on 24 infants, it was found that there was no correlation between the degree of blood destruction and the degree of icterus. Visible icterus may not be present in the infant although the icterus index may be well above 15, which is considered the threshold level commonly accepted for adults. It was found that the appearance of visible icterus was a function of the degree of hyperbilirubinemia and the length of time that the hyperbilirubinemia had persisted.

Eighty-three bromsulfalein excretion tests performed on 30 infants (from 5 to 252 hours old) showed no significant differences between those whose icterus rose to 20 or above and those whose icterus persisted below 20, with the ability of the liver of newborn infants to excrete bromsulfalein being similar to that reported for adults.

Likewise, there were no obvious differences on 96 cephalin cholesterol flocculation tests performed on 27 infants whose icterus was above or below 20. However, the degree of positivity seemed to be higher during the first few days of life, with a tendency to become negative at the end of the first week. Tests performed simultaneously on mothers during the post partum period showed results similar to the infants suggesting that the cause for both is identical and must have been in operation prior to delivery.—H. Siple.

TRUESDELL, E. D.: *Frequency and future of gallstones believed to be quiescent or symptomless.* (*Ann. Surg.*, 119, 232/, 1944.)

Direct palpation of the gallbladder was performed on 500 women during the course of abdominal operation for various conditions. In 10 per cent of the cases gallstones were felt although the patient presented no history to indicate their presence. These cases subsequently were followed up for periods of as long as 20 years or more. Only six of the 50 cases with gallstones gave negative histories up to the

present time. The gallstones apparently may be quiescent or symptomless for long periods of time; often only a single attack of pain was experienced during a period of many years. An analysis of the disposition of the fifty cases is presented.—G. Klenner.

ROBERTSON, H. E. AND DOCHAT, G. R.: *Pregnancy and gallstones: Collective review.* (*Surg. Gyn. Obstet.*, 78, 193/, 1944.)

A survey of the literature revealed that of 22,584 cases in which gallstones were diagnosed or actually found at operation, 25.6 per cent occurred in males and 74.4 per cent in females. Of 14,016 women with gallstones, 79.6 per cent had had pregnancies. Post-mortem records of 109,774 cases reported in the literature showed that gallstones were found in 5.7 per cent of the males and 12.7 per cent of the females. Before the age of 20, gallstones are rare in both sexes. However, after 20, the increase in incidence is greater in women than in men. The impression is substantiated that gallstones are more common in women than in men, that they occur earlier in women, and that pregnancy is not a major factor in their causation.—G. Klenner.

HIGGINS, G., O'BRIEN, J. R. P., STEWART, ALICE, AND WITTS, L. J.: *A clinical evaluation of some tests of liver function.* (*Brit. Med. J.*, 1, 211/ Feb. 12, 1944.)

A study was carried out on 100 healthy students and laboratory workers, 71 patients with liver diseases, and 62 patients suffering from other diseases. The clinical diagnosis in all cases was well established. Laboratory tests on these subjects included estimations of bilirubin, phosphatase, plasma albumin and globulin, hippuric acid excretion and levulose tolerance. Analysis of the results, presented in tabular form, showed that the cumulative data have considerable diagnostic and prognostic value. While all the tests gave average values in diseases of the liver which deviated significantly from the normal, they were not equally valuable in differentiating various stages of the disease. Changes in plasma proteins are of great significance. In cases of hepatitis with jaundice, a close correlation exists between the duration of the jaundice, the albumin/globulin ratios, and the prognosis; irreparable liver damage probably has occurred if jaundice persisted more than two months or if the plasma albumin fell below 2 grams percent in which case the plasma globulin usually was over 4 grams per cent.

Determination of the amount of bilirubin, phosphatase, albumin, and globulin in the plasma from a single blood specimen usually provided as much diagnostic and prognostic information as could be obtained from more elaborate tests of liver function.—E. R. Feaver.

WASCH, MILTON G.: *A new medium for gallbladder visualization.* (*Amer. Jour. Roent. Rad. Therap.*, 50, P. 400, Nov. 1943.)

A new synthetic compound commercially known as Priodax for visualization of the gallbladder was tested

on 134 cases. In the hands of the author, this substance proved more desirable than preparations of the sodium salt of tetraiodophenolphthalein. It was found to be tasteless and the reactions were generally fewer and milder. Being readily absorbed from the intestinal tract, obscuring shadows in the overlying gut were not troublesome.—H. W. Snape.

ULCER

MARTIN, LAURENCE.: *Exophthalmic goitre and peptic ulcer.* (*Lancet*, 2/5, P. 750, 1943.)

The author has found that exophthalmic goitre associated with peptic ulcer is extremely uncommon either as simultaneous or sequent events. Most patients with thyrotoxicoses have achlorhydria or hypochlorhydria, although normal acidity may return after thyroidectomy. The author questions the quoted opinion that "exophthalmic goitre may precede the onset of peptic ulcer but seldom follows it".—E. R. Feaver.

VOROBIOFF, SALOMON.: *Gastric acidity in cases of ulcers of the stomach and duodenum.* (*Rev. Med. Rosario*, 33, P. 1059, 1943.)

Results of the histamine test are noted in fifty-one patients with gastric ulcers and one hundred seventeen with duodenal ulcers. Hyposecretion and hypoacidity are more common in gastric ulcer cases, while patients with duodenal ulcers generally show hypersecretion and normal or hyperacidity. Implications of these findings, particularly in regard to gastritis, are discussed.—Biological Abstracts.

LOVE, H. R.: *Dyspeptic symptoms in soldiers.* (*Med. J. Australia*, 2, 101/, Aug. 7, 1943.)

Over a period of six months 358 soldiers were observed and the symptoms recorded. The symptoms were found to fit into five main types of classification. Pain was of two types: the "hyperchlorhydric", in which the individual responded to treatment and the "dyskinetic", in which there was no response to treatment. The hyperchlorhydric was associated with a low incidence of neurosis and a high incidence of hyperchlorhydria while the dyskinetic was associated with a high incidence of anxiety states. The dyskinetic is discussed briefly and suggestions for the control of the pain and the rehabilitation of the patient are given.—F. E. St. George.

EDWARDS, S., AND CAPEMAN, W. S. C.: *Dyspepsia: an investigation.* (*Brit. Med. J.*, 20, P. 640, Nov. 1943.)

A board of medical examiners consisting of a physician, surgeon, pathologist, psychiatrist, radiologist and a general duty officer examined 356 patients in service who showed gastrointestinal symptoms. The data were later analyzed by a statistician.

Functional dyspepsia was the most prevalent complaint and duodenal ulcer the second. The war dyspepsia was more prevalent among the non-commissioned officers than among privates. Food and alkali relieved the pain in the dyspeptics where ulcer was the underlying cause; where ulcer was not present alkali

but not food was effective in relieving distress. Sixty-five percent of the cases referred to the psychiatrist were found to have a psychological background; twenty-six of these patients had previously been operated on for "chronic appendicitis" without relief of the symptoms.—F. E. St. George.

THERAPEUTICS

SYRNEY, B.: *Prophylaxis of epidemic parotitis.* (*Pediatrics*, 1, 59/, 1943.)

Iodine was chosen because it is easily absorbed by the mucosa of the stomach, promptly reaches the salivary glands, and tends to accumulate in inflammatory foci. Three to five drops of Lugol's solution were given 3 to 4 times a day during an epidemic to all children (in institutions) with a negative or doubtful history for mumps. This procedure appeared to localize the mumps epidemic and no secondary outbreaks of mumps could be noted if prophylaxis was applied methodically.—Courtesy Biological Abstracts.

ROSENTHAL, A. S.: *Sulfanilamide and diazofulfanilamide in the treatment of dysentery in children.* (*Pediatrics*, 1 P. 31, 1943.)

During the summer of 1940, 60 children with dysentery were treated with sulfonamides. 0.2 grams of the drugs were given per kilogram of weight until improvement was achieved. Afterwards 0.15 gram per kilogram was given for several more days. The results were encouraging. In 8 cases recurrences took place after the drugs were discontinued. No toxic symptoms were seen.—Courtesy Biological Abstracts.

GLAESSNER, C. L.: *Pepsinotherapy of peptic ulcers.* (*Exp. Med. and Surg.*, V. 2, P. 175, May, 1944.)

A history of the work done on pepsinotherapy over a period of 12 years is presented.

Protein-free pepsin is injected parenterally in a series of 10 injections on successive days. The complete treatment consists of 3 of these series, each series having a greater concentration of pepsin than the preceding. It is stressed that pepsinotherapy is entirely independent of proteinotherapy. The action of the injected pepsin is believed to be due to a hormonal factor and an anti-ferment factor, the former bringing about repairment of the damaged mucous membrane and the latter bringing about increased resistance of the mucous membrane thru the production of an anti-pepsin.

Pepsinotherapy has been used with success on various kinds of ulcers. Since it brings about an increase of weight in most cases, it has been applied also by the author to cases of weight-loss from tuberculosis, malnutrition, etc. to great advantage.

Statistics dealing with results are given together with some case histories. There was an average of recurrence in about 30 percent of the cases and in 70 to 75 percent definite healing could be reported.—R. Burdick.

SMITH, H. G.: *Sulfaguanidine in treatment of Flexner dysentery.* (*Brit. Med. J.*, 1, 287/, Feb. 1944.)

Massive doses of sulfaguanidine were administered

to 44 women with Flexner dysentery. The ages of the patients ranged from 17 to 37 years. Treatment was continued until negative results were obtained on five consecutive occasions. About half of the patients developed rashes on about the ninth day of treatment. The rashes were apparently not related to the concentration of the drug in the blood. A sensitization dose of sulfaguanidine brought reactions in a number of cases although other sulfonamides did not; this would indicate that probably the guanidine radicle is the sensitizing agent.—F. E. St. George.

SURGERY

SEYBOLD, W. D., BLACK, B. M., AND JACKMAN, R. J.: *Impalement of the rectum.* (*Proc. Staff Meet. Mayo Clinic.*, V, 19, P. 224, May 3, 1944.)

The authors present a case of impalement of the rectum in a boy three years old. Eleven hours after injury the child showed no shock or hemorrhage. Examination revealed a lesion of the rectum one centimeter in diameter, and frank peritonitis in the rectovesical fossa. The temperature was 100.4° F., pulse 120, leukocyte count 13,600 (81% polymorphonuclear leukocytes). Treatment consisted of surgical repair, five grams sulfathiazole placed locally in the rectum, and administration of gas gangrene and tetanus antitoxin. Postoperative progress was steady and complete recovery attained within twenty-two days.

Impalement of the rectum may or may not involve perforation of the rectal wall or the peritoneal cavity. The mortality rate following rectal injury without perforation is 10 per cent; with visceral injury within the peritoneal cavity the mortality is more than 75 per cent if not operated. Immediate proctoscopy and a urine examination are advised except in minor injuries. Exploratory operation may be necessary when the rectal wall is lacerated or when there are signs of peritonitis or bloody urine. Retroperitoneal injury of the third part of the duodenum has been reported previously. A proximal colonic stoma may be indicated if the perineum is lacerated extensively.—E. R. Feaver.

JEWETT, H. J.: *Infiltration carcinoma of bladder; new method of ureterointestinal anastomosis employed in twenty-nine cases.* (*Brit. J. Urology*, 15, 121, Dec. 1943.)

Total cystectomy is often the only operation possible to effect cure in cancer of the urinary bladder. This radicle operation is possible only if the urine flow can be kept uninterrupted. In Jewett's two-stage operation, consisting of implantation of the ureters in the intestine and total cystectomy, the urinary passage is not interrupted. Only three of twenty-nine patients in whom this operation was performed died. The conditions suitable for this operation are briefly summarized.—F. E. St. George.

SLINE, A., SHOCK, D., AND FOGLESON, S. J.: *Healing of the abdominal wall after loop colostomy.* (*Surg. Gynec. Obstet.*, V, 78, P. 525, May 1944.)

The strength of the healing process between a colon loop and the abdominal wall was tested in 48 dogs.

Tests were performed 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, 3 days, and 5 days after operation, 6 dogs being used in each group. Tests on 6 dogs immediately after operation were also made. The extent of healing between abdominal wall and colostomy loop was measured by the amount of air pressure (in millimeters mercury) required to rupture the suture line.

The colostomy wound was found to be weakest one hour after operation. Between the first and twelfth hours the increase in strength is most marked. The healing strength drops slightly between the 12th and 24th hour but soon returns and from the 48th hour to the 5th post-operative day the healing process is of constant strength.—F. N. Chockley.

EXPERIMENTAL MEDICINE

MOTILITY

HAIDOBRO, F., MONTERO, E., AND CUEVAS, F.: *The effect of certain drugs on the motility of the jejunoleum in normal man.* (*Surg. Gynec. and Ob.*, V, 78, P. 471, May, 1944.)

Comparative studies were made of different drugs using 11 male volunteers. A Miller-Abbott tube was introduced into the intestine until the tip lay 2½ to 4½ feet below the pylorus. The tube had one end covered by a balloon, and was connected by a Marey tambour to a kymograph. Accumulated fluid above the balloon was frequently removed. With the tip in the duodenum, the subject drank 250cc. of milk, and 2 hours before the tracing was started, he took 300 gms. of clear soup. The drugs used were amyl nitrite inhalation, glyceryl trinitrate, theophylline ethyl-enediamine, methyl octenylamine, diphenyl diethyl-aminoethanol hydrochloride (trasentin Ciba), pitressin, prostigmine, atropine sulfate, and morphine sulfate, and the effects on the wave types I, II, or III compared.—Wm. D. Beamer.

GUERREIRO, J. P. AND TRINCAO, C.: *On Singer's reaction (R. R.) for proving the presence of the intrinsic factor of Castle.* (*Lisboa Med.*, V, 19, P. 1, 1942.)

The authors tested Singer's method for proving the presence of Castle's intrinsic factor in human gastric juice: the rise of reticulocytes in the peripheral blood of white rats after injection of non-heated juice. They found the normal much higher than did Singer whose rats did not show a reticulocytosis of more than 4 per cent. The numbers were similar to those of Ortiz Picon who observed in Spanish rats a reticulocytosis of 4 to 30 per cent. The authors believe a climatic factor may interfere. Then, too, one animal varies, markedly from another. This does not lessen the value of this finding since the results are as distinct in animals with low reticulocytosis as in those with high. The quantity of injected juice also is unimportant. Confirming Singer's results, all heated juices gave a negative reaction except one in which the time of heating probably was insufficient. In normal subjects and in those with various stomach diseases the gastric juice showed the presence of Castle's enzyme; in 5 subjects with pernicious anemia, the enzyme was absent.—Courtesy Biological Abstracts.

PATHOLOGICAL CHEMISTRY

DILLARD, G. H. L., SPENCE, H. Y., AND FORBES, J. C.: *Effect of food on liver fat of animals following carbon tetrachloride poisoning.* (*Virginia Med. Month.*, 71, P. 154, 1944.)

Administration of glucose or sucrose prior to anesthesia of rats with carbon tetrachloride has no effect in preventing fatty hepatic infiltration twenty-four hours later. Administration of these substances for twelve hours following such anesthesia reduced or prevented fatty infiltration. Ammonia acids had no such effect. Hepatic necrosis is also diminished by feeding for two days or more after anesthesia, as compared to starved controls. Comparable results were obtained on dogs, and with chloroform anesthesia in rabbits. Evidently, an adequate caloric intake following administration of these toxic agents is of benefit in preventing hepatic fatty infiltration and necrosis. They suggest that administration of carbohydrate facilitates hepatic regeneration by preventing fatty infiltration.—Courtesy Biological Abstracts.

CALANDRA, J. C., FANCHER, O. E., AND FOSDICK, J.: *The effect of synthetic vitamin K and related compounds on the rate of acid formation in saliva.* (*J. Dental Research*, V. 23, P. 31, February, 1944.)

Certain quinones and derivatives were tested to find their possible inhibitory effect on acid stimulation. Saliva was collected and divided into portions. On one portion of fresh saliva a calcium determination was done as a control. To the other portions were added glucose and powdered human tooth enamel and the test material. These as well as the control samples were incubated with constant agitation for 4 hours, at the end of which time calcium determinations were made on all samples. It was found that all the quinones and derivatives inhibited acid formation; 2-methyl-1, 4 naphtho-quinone was found to be as effective as any others tested and often superior. The authors also found that various peroxides were effective in inhibiting acid formation.—I. M. Theone.

PHARMACOLOGY

SCUDI, J. V., JELINEK, V. C., AND KUNA, S.: *Biochemical aspects of the toxicity of atabrine. I. Acute effects of massive doses on the rat.* (*J. Pharmacol. and Therap.*, V. 80, P. 144, 1944.)

The mortality of a single dose of atabrine was increased in the rat from zero to forty-eight per cent by causing the animals to fast for increasing lengths of time. This dose caused a severe irritation of the gastrointestinal tract resulting in a flow of fluid into the stomach and intestines. The distention was followed by diarrhea. There is a marked hemo-concentration, a loss of blood chlorides and a severe loss of blood bicarbonates. Similar results were obtained with a smaller dose of the drug (twenty per cent of the lethal dose 50). The larger dose of the drug produced a severe liver necrosis. As judged by the retention of

bromosulfalein and prolongation of the prothrombin time. Inhibition of liver function was produced by the drug and this inhibition was increased by fasting. Plasma fibrinogen concentrations were increased appreciably by the administration of atabrine.—Biological Abstracts.

MISCELLANEOUS

LAST, M. R., AND LAST, J. H.: *The internal biliary fistula dog unsuitable as a bioassay animal for liver extract.* (*Proc. Soc. Exp. Biol. and Med.*, V. 54, P. 46, Oct., 1943.)

Biliary fistulae were produced in dogs. In 4 to 6 months following the operation, a mild macrocytic, hyperchromic anemia appeared, characterized by spontaneous remissions and relapses not associated with reticulocyte showers. Blood chemistry values were normal.

In the dogs receiving liver therapy there was no reticulocyte response of significance, nor was there a maintained rise in the erythrocyte count. The lack of response of the peripheral blood picture to liver therapy may be explained by the fact that bone marrow sections showed no megaloblastic bone marrow characteristic of pernicious anemia.

Because of the spontaneous variations during the anemic period and the indefinite nature of reticulocyte and red blood cell increases following liver therapy, it is concluded that this method is impractical as a means of bioassay of liver extracts.—R. L. Burdick.

FENNEL, E. A.: *Amylase determinations.* (*Am. J. Clin. Path.*, V. 14, P. 89, February, 1944.)

Because the test presented is rapid and accurate, the author believes that it may be of great diagnostic value in cases of mumps, simple pancreatitis, necrotic pancreatitis and similar conditions. To prove its diagnostic value, 46 brief case histories are given.—R. L. Burdick.

MERENDINO, K. A. AND LITOW, S. S.: *A "Lucite" gastrostomy tube for pouch dogs and possibilities for applications in man.* (*Surgery*, V. 15, P. 326, Feb. 1944.)

Previously many different types of cannulas have been devised of various materials for collection of gastric pouch juice in dogs. None have been completely satisfactory due to 1) tissue irritation caused by the material used, 2) removal of the cannula by the experimental animal, and 3) seepage about the gastrostomy tube.

The authors describe a lucite gastrostomy tube for pouch dogs. The advantages claimed for it are: 1) it cannot be removed by the dog, 2) if the rubber tubing is pulled off it can be replaced easily without risk to the animal, 3) it is watertight, and 4) it has the physical and chemical advantages of lucite with workable properties satisfactory for use in tissues. A note is appended concerning its possible applications in man e.g. in gastrostomy, cystostomy, hernial defects, etc.). —E. F. Feaver.

Physiological and Clinical Aspects of Ketosis*

By

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IT IS now generally agreed that under conditions leading to ketosis, acetoacetic acid is the first ketone body to be formed (2). It is known that various tissues of the mammalian organism are able to reduce acetoacetic acid to beta-hydroxy-butyric acid and also to effect the reverse reaction. Acetone is readily formed in solutions containing acetoacetic acid and it is generally assumed that whenever it is found in biological fluids it is merely a spontaneous decomposition product which indicates that an equivalent amount of one of the other ketone bodies was formerly present.

SITE OF ORIGIN OF THE KETONE BODIES

Practically all investigators have agreed as to the chief source of the ketone bodies which appear in the blood. Embden (3) (4) and later Snapper and Grunbaum (5) (6) perfused livers, kidneys, lungs and skeletal muscles and found that only the liver produced significant amounts of the ketone bodies. A similar conclusion regarding ketogenesis by these organs *in situ* was reached by Hinrich and Goldfarb (7) (8) who compared the ketone levels of the inflowing arterial blood and the outflowing venous blood of various organs in the intact animal. However, they found the occasional output of small amounts of ketone bodies from the skeletal muscles and the intestinal tract. In agreement with this Jowett and Quastel (9) found that slices of kidney, spleen, testes and brain, when studied *in vitro*, could produce small amounts of the ketone bodies from butyric acid, although liver slices under similar conditions produced 10-40 times as much.

Whether or not the extrahepatic tissues can under special experimental conditions be shown to form some ketone bodies it is clear that, in the living intact animal, the liver is practically the sole source for these substances. Thus it has been demonstrated that dogs in which the functional capacity of the liver is limited by an Eck fistula do not exhibit an increased ketosis upon phlorhization (10). The reduction of liver function by hepatotoxic agents also decreases the rate of appearance of ketone bodies in the poisoned animals (11). A comparison of the rate of disappearance of administered Na acetoacetate in intact and eviscerated normal and diabetic dogs by Chaikoff and Soskin (12) showed that the initial ketosis of intact diabetic animals was due to rapid ketogenesis in the liver. Finally Mirsky (13) has recently shown that the ketogenic effects of certain pituitary extracts which are regularly obtained in normal animals cannot be demonstrated in the absence of the liver.

SOURCE MATERIALS FOR KETONE BODY PRODUCTION

The early work of Embden and co-workers (14) (15) indicated the formation of extra ketones by the perfused livers with which he worked, when either fatty acids, certain amino acids, or pyruvic acid were added to the perfusing fluid. These three different source materials for the ketone bodies have since been confirmed by a number of investigators in a variety of ways (2) (9) (16) (17) (18) (19). However, Embden reported that the amount of ketone bodies arising from fat greatly exceeded that from the other sources. Subsequent work has emphasized the fact that when ketosis occurs in the living organism it may be regarded, for practical purposes, as an index of the catabolism of fat in the liver. Thus the perfused fatty liver produces much more ketones than the liver which is poor in fat (20). The livers of depancreatized or phlorhizinized animals which are characteristically rich in fat, are known to produce excessive amounts of the ketone bodies (21). In the intact normal animal the feeding of fat, or the excessive use of depot fat induced by starvation, results in ketosis. More recently Stadie et al (22) have demonstrated that the production of ketones by liver slices *in vitro* is accompanied by the disappearance of amounts of fatty acid sufficient to account for the ketone bodies formed (23).

MECHANISM OF KETONE BODY PRODUCTION

Our conception as to the mechanism by which ketones are formed from fatty acids seemed for a long time to be quite settled, but has more recently undergone at least two metamorphoses. The theory of successive beta-oxidation originated from the work of Knoop (24). He concluded that the fatty acids were degraded by the splitting off of two carbon atoms at a time, by oxidation at the carbon atom which occupied the beta position to the carboxyl group. It was assumed that the acetic acid molecules so formed were rapidly metabolized leaving the last four carbons in the chain, which underwent oxidation at the beta position but were not split. (Fig. 1) It was therefore assumed that each molecule of an even-numbered fatty acid regardless of chain length resulted in the production of one molecule of ketone, and that odd numbered fatty acids could not give rise to ketone bodies. On this basis also the amount of oxygen required for the degradation of a given fatty acid and the production of one molecule of ketone could be calculated.

Although this conception gained wide popularity (especially amongst clinicians concerned with clinical states characterized by ketosis) and although it persists in many textbooks up to the present day, serious

* The material relating to the physiological aspects of the subject is an abbreviated version of a previously published review (1).
The clinical material is new.

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Until recently the multiple alternate oxidation theory was adequate to explain the available data. However, in a systematic *in vitro* study of the ketogenic properties of fatty acids consisting of 1-11 carbon atoms, Jowett and Quastel (2) (9) noted amongst other things, ketone production from valeric acid (C_5)

of two acetic acid molecules, a process which has been known since the days of Friedmann (33). Friedmann's observation was made on isolated livers perfused with solutions containing acetic acid. Recently Barnes et al (34) using acetic acid containing heavy carbon, conclusively demonstrated the chemical reaction in *in vitro* experiments. The hypothesis of MacKay and co-workers seems to be the most reasonable explanation of the known facts at the present time.

We have seen that for practical purposes the liver may be regarded as the chief if not the only source of ketone bodies in the intact organism. The extent

(Palmitic Acid)

$$\begin{array}{ccccccc} \text{CH}_3\text{CH}_2 & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. \\ \text{CH}_3\text{COOH} & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{COOH} \end{array} \right. \quad (\text{Acetic acid}) \\ \text{CH}_3\text{CO}\cdot\text{CH}_2\cdot\text{COOH} & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. & \left\{ \begin{array}{c} (\text{O}) \\ | \\ \text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOH} \end{array} \right. \\ \text{C}_{16}\text{H}_{32}\text{O}_2 + 7 \text{ O}_2 \rightarrow 8 \text{ C}_2\text{H}_4\text{O}_2 \rightarrow 4 \text{ CH}_3\text{CO}\cdot\text{CH}_2\cdot\text{COOH} + 4 \text{ H}_2\text{O} \\ 1 \text{ mol palmitic acid} + 7 \text{ mols } \text{O}_2 \rightarrow 8 \text{ mols acetic acid} \\ 8 \text{ mols acetic acid} \rightarrow 4 \text{ mols acetoneacetic acid} \\ 1.75 \text{ mols } \text{O}_2 \text{ per mol of acetoneacetic acid} \end{array}$$

and a greater production of ketones from hexanoic (C_6) than from butyric acid, (C_4). Since valeric acid (C_5) is known to give rise to sugar through propionic acid (C_3) one can account for the ketone formation only by assuming a condensation of a two-carbon atom fragment from one molecule of valeric acid with a similar two-carbon atom fragment from another molecule. The condensation of such two-carbon atom fragments (acetic acid) could also account for the greater ketone formation from hexanoic than from butyric acid. Leloir (19) has recently confirmed these findings of Jowett and Quastel, and MacKay and co-workers (31) (32) have recently performed feeding experiments on intact animals which support the above interpretation and which led them to postulate a new theory which they termed the "beta-oxidation-acetic acid condensation hypothesis". (Fig 3).

They found in brief that the feeding of propionic acid (C_3) to their animals led to an accumulation of liver glycogen without ketone body formation. The feeding of valeric acid (C_5) led to both glycogen and ketone body formation. Heptanoic acid (C_7) gave rise to glycogen and to more ketones than did valeric acid. MacKay et al postulated that all fatty acid chains, whether odd or even, were subjected to oxidation at each alternate carbon atom. However, the molecule then split at every keto group to form a number of acetic acid molecules, except where a three-carbon atom fragment remained to form propionic acid. (This of course resembles in part the original beta-oxidation theory, although there is little basis for deciding between successive or simultaneous oxidation and splitting). Ketones are formed by the condensation

to which ketones accumulate in the blood or are excreted in the urine will of course depend upon whether or not they can be disposed of by the extra-hepatic tissues, and how rapidly such utilization may occur. Some of the earlier investigators regarded the ketone bodies as abnormal intermediary products of fat metabolism, which appeared only when there was a failure in carbohydrate oxidation. It was thought that under these circumstances the ketones could not be metabolized because of the supposed absence of a coupled oxidation phenomenon which ordinarily occurred (35) (36). *It is now well recognized that ketosis occurs under conditions in which large amounts of carbohydrate are being oxidized*, and indeed it has been impossible to demonstrate any relationship between the degree of ketosis and the rate of carbohydrate oxidation (37) (38) (39) (40). On the other hand there is ample evidence that both acetoacetic acid and beta-hydroxybutyric acid are catabolized to $\text{CO}_2 + \text{H}_2\text{O}$ by kidney, muscle, heart, testes, etc., as tested on isolated slices *in vitro* (2) (9) (29) (41). Similar evidence is available for perfused whole organs such as muscles or kidneys (42) (43). The rate of utilization of the ketone bodies by the normal intact organism has been estimated by a number of investigators (44) (45). It is important to note that this utilization, at the blood concentrations of ketones ordinarily found in clinical ketosis, may constitute a very significant portion of the total energy requirements of the organism. Indeed it has been estimated that the ketone utilization in the animals which have been studied could account for 50-80 per cent of the total oxygen consumption.

Despite the large capacity for the utilization of

TABLE I
Causing Factors in Various States of Ketosis

CLINICAL STATES	References	Deficient CHO Intake	Excess. Glycogenolysis	Disturbed Glycogenesis	Excess Demand for CHO	Abnormal Glycogen	Relative or Absolute Insulin Lack	Ant. Pituitary Excess	Adrenal Cortical Excess	Female Sex Hormone Excess	Alkalosis	Dehydration
Starvation	62, 63	+						?				
High Fat Diet	64, 65	+						?			+	
Excessive Vomiting	66, 67	+									+	+
Alkalosis	68, 69 70											
Fever and Infectious Diseases	71	+	+	+	+							+
Anesthesia	72		+	+								
Hepatitis and Early Cirrhosis	73, 74		+	+								
Advanced Circulatory Failure	75		+	+								
v. Gierke's Disease	76, 77					+						+
Diabetes Mellitus	78, 79		+	+				?	?			
Acromegaly	80						+	+				
Adrenal Cortical Hyperfunction	81								+			
Hyperthyroidism	80			+								+
Pregnancy and Menstruation	82, 83							?		+		
Violent Exercise	84					+						+

DISURBANCES
IN
FOOD INTAKE

IMPAIRMENT
OF
LIVER FUNCTION

ENDOCRINE
DISORDERS

ketones in the normal organism, it might be supposed that diabetes, phlorizin poisoning or starvation cause some difficulty in the utilization of ketones by the periphery. This possibility has been tested both *in vitro* and *in vivo* without confirmation. Chaikoff and Soskin (12) and others (29) (38) (42) (43) have shown that the peripheral tissues of the diabetic organism dispose of the ketone bodies as rapidly as do those of the normal animal. With the possible exception of the adrenalectomized animal (46) it must be assumed that whenever ketones appear in excess in the blood and other tissues, this condition is due to a rate of formation and secretion by the liver sufficiently rapid to exceed even the large disposal capacity of the periphery. It is thus no longer proper to speak of antiketogenesis in the sense so long employed by clinicians, by which they actually meant ketolysis (oxidation of ketones). In view of our present knowledge the various ketogenic and antiketogenic ratios (36) which have been used to calculate the amounts of carbohydrate "necessary for the oxidation of the ketone bodies," must be regarded as being without any real significance. The former clinical utility of these rule-of-thumb ratios was purely coincidental.

It is clear that the regulation of the ketone bodies in the intact organism must depend upon factors which either increase or decrease the rate of formation of these substances by the hepatic cells, as indeed the terms ketogenesis and antiketogenesis imply. The array of evidence for the supposed ketolytic action of carbohydrate, marshalled by Deuel and co-workers, has been amply refuted by MacKay in his recent review (47). It is necessary, therefore, to interpret those conditions or substances which increase or decrease ketosis, in terms of their effects upon the liver. The commonest conditions under which significant ketosis occurs are: starvation in the normal organism, and experimental or clinical diabetes. Both conditions are accompanied by low levels of liver glycogen and an increased fat content. Whether or not the glycogen level itself is the critical factor or is merely a reflection of increased glycogenolysis (48) (49) (50), it may be supposed that under these conditions carbohydrate yields to fat as the chief substrate for oxidation by the hepatic cells. This might be regarded as a simple mechanical result—the fat filling the space no longer occupied by glycogen—or might perhaps be more accurately described as the establishment of the predominance of fat in the competition for available oxygen, according to the evidence brought forward by Edson (30) and by Jowett and Quastel (2) (9). Carbohydrate which is the most readily available source of liver glycogen and which clears the liver of excessive fat, is the chief antiketogenic foodstuff. The antiketogenic action of protein may be similarly explained in accordance with its glycogenic and lipotropic properties. The inferior antiketogenic potency of protein as compared with carbohydrate may depend upon the fact that some of its constituent amino acids are ketogenic.

The work of Jowett and Quastel (9) and of Cohen (16) has suggested another type of mechanism for

antiketogenesis, namely competition for the enzyme system concerned with the conversion of fatty acids to ketones. These workers have shown that certain substances with "active" groups similar to those possessed by the even-numbered fats may attach themselves to, and thus compete for, the above enzyme system. If these substances themselves produce no ketones, or less ketones than are produced by equimolar amounts of the even-numbered fats, the net result will be a diminution of ketogenesis, even though some of these substances would themselves be ketogenic in action, if given at a time when the enzyme system was unoccupied. Such substances are: odd-numbered fatty acids, certain amino acids, benzoic, cinnamic, and alpha-amino butyric acids, etc.

ENDOCRINE REGULATION OF THE KETONE BODIES

Our knowledge of the endocrine regulation of the ketone bodies is as yet quite fragmentary. Practically every endocrine gland can be involved on the basis of one or another piece of evidence, but such links are usually vague. Thus Deuel and co-workers (51) (52) have shown a sex difference in rats as regards the degree of ketosis manifested under similar conditions, from which one might conclude that the gonads perform some unknown function in this regard. It may be, of course, that this sex-difference depends upon the sexual variation in the activity of the anterior pituitary gland and is not a direct result of gonadal activity. It is also known that both the thyroid hormone (53) and the secretion of the adrenal medulla (54) exert a ketogenic influence. Their actions have chiefly been observed under conditions in which their administration has aggravated the ketosis resulting from other circumstances. Since both these hormones increase the rate of hepatic glycogenolysis, their ketogenic action may perhaps be regarded as being secondary to this phenomenon. At any rate no mechanism for a more direct action of these substances is known.

Of the endocrine factors involved the three about which we have some definite information are, on the one hand, insulin which is antiketogenic and, on the other hand, the anterior pituitary and the adrenal cortex which are ketogenic. That these glands are truly antagonistic in action as regards ketosis seems clear from the facts that:

- 1) Anterior pituitary extract will cause a rise in the ketone bodies of the blood even in the normal animal, in which amounts of insulin adequate for ordinary purposes are present (55) (56).

- 2) The administration of additional insulin to a normal animal prior to the administration of anterior pituitary extract, diminishes or abolishes the ketosis which would otherwise be precipitated (55) (56).

- 3) The action of both insulin and the anterior pituitary in regard to ketosis have been shown to be exerted largely upon the liver since neither is effective in the liverless animal (13) (56). It must be concluded that here again the regulatory action is on the production of ketone bodies and not on their utilization.

The pancreas and the anterior pituitary also exert opposing actions on a phenomenon outside the liver which probably has an important effect on ketogenesis, namely, the mobilization of fat from the peripheral depots. The uncontrolled human diabetic, and the depancreatized animal without lipotropic deficiency, both exhibit hyperlipemia and fatty infiltration of the liver. The administration of insulin inhibits this mobilization of fat to the liver (57). On the other hand, certain extracts of the anterior pituitary gland have been shown to cause a hyperlipemia by liberation of fat from the depots (58). Thus insulin and the anterior pituitary might be supposed not only to exert opposing influences on the hepatic catabolism of fat to ketone bodies, but also to regulate the supply of fat to the liver for this catabolism. However, the intimate nature of the chemical mechanisms involved in these actions is unknown, and there is a possibility that at least a portion of these effects is indirect, through changes in carbohydrate metabolism. Thus, insulin which raises the liver glycogen in the diabetic animal, simultaneously inhibits the ketosis. In the normal animal in which insulin usually causes a fall in liver glycogen, it may also stimulate ketosis (59). As regards the pituitary there is some evidence that a continued high carbohydrate intake depresses the activity of this gland (59). It is thus possible that the lack of carbohydrate intake in the fasting animal leads to an increased activity of the anterior pituitary and that this in turn is responsible for both the lipemia and the ketosis of fasting.

As regards the adrenal cortex, about all that one can say at the present time is that it acts similarly to the anterior pituitary gland. Since large amounts of the extracts of each of these glands have been shown to be effective in the absence of the other gland, they may act independently of each other. However, the striking lack of ketosis in the hypophysectomized animal does indicate the predominating influence of the pituitary gland over the adrenal cortex in the overall regulation of the intact animal (60) (61).

We may summarize by saying that the ketone bodies are probably normal intermediates of fatty acid catabolism in the liver. They appear in excess in the blood whenever the hepatic metabolism of fat is sufficiently speeded up, either by a lack of carbohydrate substrate or by disturbance in the normal regulation of the substrate mixture. The ketone bodies are readily utilized by the peripheral tissues, under practically all known conditions.

CLINICAL KETOSIS

Table I lists the abnormal physiological states and the clinical conditions in which ketosis is encountered. It also indicates the particular causative factors involved in each instance. As we have seen from the previous discussion, the fundamental disturbance underlying all ketosis is a relative or absolute lack of carbohydrate in the liver, leading to an excessive breakdown of fat. However, the conditions leading to this fundamental disturbance can be divided into three sub-groups according to the manner in which

it is brought about, namely: (a) disturbances in food intake; (b) impairment of liver function and (c) endocrine disorders. It will be noted that there are a number of question marks in the table. These are applied to certain of the endocrine mechanisms to indicate not only our fragmentary knowledge as to the way in which they operate, but also our lack of complete assurance that they operate at all in a particular condition. With these reservations, however, Table I completely relates clinical ketosis with our previous physiological considerations. Certain key references to more detailed consideration of the several conditions are also included in the table.

Von Gierke's disease and diabetes mellitus require some additional comment. The former is exceptional in that it is the only condition in which ketosis is associated with large stores of glycogen in the liver. But this glycogen is not available for use as is also evident from the fact that there is a low blood sugar level. In the table the glycogen in von Gierke's disease was therefore labelled "abnormal". In reality it is more likely that the glycogen itself does not differ from that found in normal livers but that the hepatic enzyme systems are abnormal, with a consequent inability to mobilize the glycogen. The net result as far as the organism is concerned is the same as if the glycogen were absent. As regards diabetes mellitus it will be noted that the factor of insulin lack is designated "relative or absolute". This is because, unlike experimental pancreatic diabetes, we still do not know whether in human diabetes mellitus there is an actual deficiency of insulin or whether there is an excess of opposing endocrine factors. From the practical therapeutic viewpoint this of course makes little difference, since in either case the administration of exogenous insulin will temporarily restore the disturbed endocrine balance.

SECONDARY EFFECTS OF KETOSIS

It is not at all certain whether the occurrence of ketone bodies in the blood and urine is in itself harmful. The evidence as to the toxicity of acetoacetic acid is contradictory to say the least (71). Be that as it may, it is clear that the appearance of the ketones in excess of the amounts which can be metabolized by the peripheral tissues sets into motion a vicious cycle with a number of harmful secondary effects. The fact that they are organic acids necessitates their neutralization by sodium to preserve the normal pH range of the blood and to enable their excretion by the kidney. The ketonuria is therefore accompanied by a loss from the body of fixed base and water. Further loss of Cl results from the vomiting which often accompanies ketosis. All these factors lead to dehydration and hemoconcentration which, together with the loss of salts, results in an impairment of kidney function. When this occurs the ability of the body to metabolize and otherwise deal with the keto acids rapidly diminishes and there begins a shift in the pH of the blood to an extent incompatible with consciousness and life.

The postmortem findings, in individuals in whom

ketosis was the predominating cause of death, support our analysis of the pathological physiology. There are no specific organic lesions to be found. There is a cerebral capillary dilatation, perivascular edema and acute degenerative changes in the cells of various parts of the central nervous system. The findings in other parts of the body are those which are also seen in acute exsanguinating hemorrhage and in congestive heart failure. In general therefore the tissue pathology might very well be accounted for by dehydration, hemoconcentration and cerebral anoxia.

THE TREATMENT OF KETOSIS

For purposes of treatment another classification of states of clinical ketosis may be made, namely:—Diabetes mellitus on the one hand and all other conditions on the other hand. Diabetes is the only condition in which the original disturbance is a relative or absolute lack of insulin, and in diabetes the most essential part of the treatment is the early, adequate and persistent administration of insulin. This treat-

hemoconcentration and hypochloremia can affect the liver to a degree where it cannot use the carbohydrate which is being proffered to it. Thus when these complications of ketosis have advanced to any considerable degree, their relief may be quite as urgent a matter as the administration of insulin in diabetes, and of carbohydrate in non-diabetic ketosis. In these advanced states, therefore, the therapy of the primary derangement and its complications must be simultaneous rather than consecutive.

To revert to the classification in Table I for some comment about particular states of ketosis, the conditions listed under "Disturbances in Food Intake" can in general be corrected by normalizing the intake. The acetonemic vomiting of children and that of pregnancy present special problems which may have to be overcome by the parenteral administration of carbohydrate and fluids until the vicious cycle is broken.

The conditions classified under "Impairment of Liver Function" (von Gierke's disease excepted)

FIG. 4

Carbohydrate Required to Restore a Comatose Diabetic Person to Normal by the End of the First Twenty-Four Hours of Treatment with Insulin

Subject: A man weighing 70 Kg., with a liver weighing 1,500 Gm., muscle weighing 35 Kg. and 21 liters of blood and extracellular fluid.		
	Diabetic Gm.	Normal Gm.
Liver glycogen	9 (0.5 %)	105 (6.0 %)
Muscle glycogen	70 (0.2 %)	245 (0.7 %)
Extracellular sugar	74 (0.35 %)	17 (0.05 %)
	153	370
		157
Carbohydrate requirement for replenishment of stores, Gm		217
Carbohydrate requirement for 24 hour utilization, Gm		201
(based on 50% of 2,100 calories)		
Total, Gm.....		418

ment will of course be rendered more effective by the simultaneous administration of adequate amounts of carbohydrate, water and salt. But the need for the hormone is paramount.

It is equally important to remember that in non-diabetic ketosis the administration of insulin can do no good and may do harm. The cardinal principle of the therapy of ketosis is to supply ample carbohydrate to the liver under conditions in which this organ can store it as glycogen. Insulin is necessary to accomplish this purpose in the diabetic organism. The non-diabetic organism already has an optimal amount of insulin available for this purpose, and any exogenous insulin which is administered is in excess of this optimal amount. Excess insulin has been shown to lower the level of glycogen in the normal liver and when administered with carbohydrate will result in a smaller increase in liver glycogen than would have been caused by giving the same amount of sugar alone (86). In this paradoxical sense then, administered insulin may be regarded as a ketogenic factor in the normal animal and should not be used in the treatment of non-diabetic ketosis.

The operation of the vicious cycle initiated by ketosis must be kept in mind constantly, for the dehydration,

present the special difficulty that it may require very high concentrations of sugar in the blood to secure adequate hepatic storage of glycogen (87). It is sometimes possible to effect the necessary hyperglycemic level only by the intravenous administration of the sugar. As regards the ketosis which may accompany fever, the infectious disease, anesthesia and advanced circulatory failure, prevention is of course much better than cure and there are ample references in the literature to the value of a high carbohydrate regimen in these conditions. Nothing is known concerning the treatment of von Gierke's disease but, fortunately, ketosis is not an important part of this syndrome.

Of the endocrine causes of ketosis, diabetes mellitus is the only one of clinical significance. The paramount importance of insulin therapy in this type of ketosis has already been stressed.

When carbohydrate administration to supplement insulin therapy is advocated for the treatment of diabetic coma, it is often objected that the comatose person is already saturated with sugar, so that the administration of more carbohydrate is useless. A little simple arithmetic will show that this concept is erroneous (Fig. 4). The stores of glycogen of such a person are negligible. The available carbohydrate is chiefly that which is

present in the blood. The accompanying calculation clearly shows the inadequacy of this extracellular sugar, as compared to the amount necessary to replenish his stores of glycogen and supply his caloric requirements, as the carbohydrate metabolism reverts to normal under the influence of insulin.

It is evident that almost 500 gm. of carbohydrate must be administered to this hypothetical person during the first twenty-four hours of treatment and about one-half of that amount during subsequent days in order to maintain normal stores of glycogen and carbohydrate metabolism.

The clinical literature on the treatment of ketosis, and of diabetic ketosis in particular, contains a number of suggested systems of treatment which specify the amounts of insulin, carbohydrate, water and salts and the intervals for their administration favored by the particular author. Each and all of these systems of treatment are good if followed conscientiously, with

an understanding of the basic principles involved, and until the desired ends are attained. Insofar as all systems of treatment tend to become mechanical and are apt to be followed routinely without individualization for the special needs of a particular patient, they are all bad. For example a diabetic child with an infection who has been precipitated into coma within 24 hours, may require much insulin and sugar but little fluid or salt. A mild elderly diabetic on the other hand may go into coma as a result of weeks of neglect of treatment, during which time there is extreme loss of water and salts. It is therefore not the intention of the present authors to offer another system for the treatment of diabetic coma. Instead it is urged that with the physiologic facts in mind treatment be directed towards the various factors which have been outlined, and that the treatment be vigorous, continuous and maintained until the simple clinical and laboratory evidences of ketosis, dehydration, hemoconcentration and hypochloremia have been abolished.

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The Differential Diagnosis of Glycosuria

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THE finding of glycosuria is a fairly common occurrence. Once found two possibilities present themselves: first, is it a diabetic glycosuria, or second, is it a non-diabetic glycosuria? From the standpoint of the clinician and the welfare of the patient, only these two categories require consideration. Other causes for glycosuria are of purely academic interest and do not enter into the problem.

If such a glycosuria is diabetic in origin it demands immediate investigation and prompt intervention. On the other hand if the glycosuria is non-diabetic, it can be dismissed. If it is due to early diabetes, the patient must not be allowed to drift into a more advanced and serious state. It is the early case of diabetes that can be controlled with a minimum of adjustment and thus prevent a progressive deterioration of the islands of Langerhans. If this deterioration is allowed to occur, the disease becomes more severe and the therapy more difficult. Early treatment of diabetes mellitus is preventive medicine of the highest order.

The finding of glycosuria presents a definite challenge to the physician, for in diabetes he is confronted with a real medical problem requiring attention, whereas in non-diabetic glycosuria there is no problem. This is emphasized, as long periods of medical meddling in instances of non-diabetic glycosuria are inexcusable. It is not remarkable that those individuals are mentally disturbed when they find out their real status.

Let us take such a case of glycosuria just discovered in a doctor's office and follow it through to its final disposition. It is 9 A. M. when sugar is discovered in the urine. What is the next step? A very simple routine will solve the problem. Have the patient eat a heavy carbohydrate lunch at 11:30 A. M., and note the exact time he started eating. Then two and a half hours from this time determine the blood sugar. Approximately two cubic centimeters of blood is adequate for this examination and should be obtained with a two cubic centimeter hypodermic syringe, found in any doctor's bag. A pinch of Sodium or Potassium oxalate in the tube will prevent coagulation if the tube is inverted a few times. A laboratory will have the answer in less than one hour. If the blood sugar is below 120 mg per cent, the patient is non-diabetic. If the blood sugar is above 120 mg per cent, he is probably a diabetic. If it is well above 120, say 200 or more, there is no question,—a frank diabetes exists. If, on the other hand it is 126 or 136, one needs to go into the problem further and do a glucose tolerance test the following morning. One hundred gm. of glucose is given orally after a night's fasting and blood and urine are obtained before and one half, one, two, and three hours after the administration of the glucose. The resultant curve will allow a definite decision. If the curve descends in two and a half hours to 120 mg. per cent or below, the patient is not diabetic; if it is 200 or more at two and a half hours, the patient is a frank diabetic; if it is 126 to 136, then we are dealing

with a potential or pre-diabetic state. This latter circumstance is most interesting from a medical standpoint, for such a case presents a challenge to the physician. Can he be kept from developing a frank diabetes as the years go by or will he eventually slip into the diabetic fold? Here is a real chance for the practice of significant preventive medicine. All that is necessary is slight restriction of diet which eliminates the excessive use of carbohydrates or overeating and periodic annual examination.

Much of the orthodox teaching in regard to glycosuria has been fallacious and has produced confusion and blunders. It is essential that a more rational view be taken. Teaching from theory and teaching from practice should be one, as both deal with the same problem and a closer correlation is needed.

Whether or not glycosuria is found in any one individual depends on several things; first, the renal threshold for sugar, second, the length of time from the last meal and from the last urination, and third, the height of blood sugar at the time (and just preceding) the urine is examined. All three of these conditions must be taken into consideration to prevent misinterpretation of the significance of glycosuria. We will have no knowledge of the first when we find glycosuria. To determine this, one needs a glucose tolerance test. The second can easily be ascertained by questioning. The third will not be known but can be ascertained later (the glucose tolerance test).

The renal threshold for sugar is not the same in all individuals. It varies tremendously. It may range from 65 to 450 mg. per cent (Table 1). This is important to bear in mind. Since there is such a wide variation in the renal threshold, how can one estimate the threshold of a particular individual? This is impossible. For that reason the glucose tolerance test is needed. On the other hand it is not essential to know the patient's exact renal threshold. All that is necessary and all that is of any importance is: Is he, or is he not a diabetic? That can be ascertained from the two and a half hours post-prandial blood sugar test with minimal loss of time and expense to the patient. There is no indication for doing a glucose tolerance test if the two and a half hours post-prandial blood sugar is 200 mg. per cent or more, for the glucose tolerance test will give no more information. It is already known that the patient is a diabetic. The extreme height and prolongation of the curve if it starts with a normal blood sugar or a near normal is not an index to the severity of the patient's diabetes. Some patients with the most abnormal glucose tolerance curves turn out to be the mildest diabetics.

As to symptoms, again we are on thin ice. A patient with glycosuria may have most or all of the cardinal symptoms of diabetes (case 10) and not be diabetic; or he may have none of the symptoms and be a diabetic. The following case is an outstanding example of the latter. A woman past fifty years of age, pre-ented herself for examination, not knowing that she had diabetes. She had no symptoms of any kind, neither then or at any time previously, but her blood sugar was 850 mg. per cent. This was con-

firmed by further examinations. After her hyperglycemia was controlled she required 35 units of insulin daily on a 2000 calorie diet. She needs no more to this date. This illustrated forcibly the necessity of being on the alert for faulty interpretation of symptoms or lack of symptoms.

Symptoms alone prove nothing. It is the laboratory evidence which is of diagnostic value, regardless of the presence or absence of symptoms. One can be easily misled if he finds classical symptoms and a glycosuria. That WAS the old teaching. But, it is faulty, it MISSES the crucial point of differential diagnosis and should be guarded against.

If one ascertains the presence of a non-diabetic glycosuria, how sure can he be that it will remain that for the rest of the patient's life? There are statements in the literature that any patient with glycosuria is apt to become a frank diabetic. When one examines these data critically, it becomes obvious that the original diagnosis of non-diabetic glycosuria was based on faulty premises and on inadequate laboratory evidence. All that can be done with such information is to disregard it. If one starts with cases where the original diagnosis of non-diabetic glycosuria was based on adequate evidence, it is found that a patient with a non-diabetic glycosuria does NOT drift into diabetes. Here one also must use discrimination. In our population we have from one to two per cent who are diabetic. A case of non-diabetic glycosuria is not exempt from this incidence. If a patient with proven non-diabetic glycosuria is shown to have diabetes in later years, this is probably fortuitous and will occur in one to two per cent of such patients. If non-diabetic glycosuria were a precursor of diabetes, a high percentage of these patients would develop diabetes. That is not the case for several hundred such cases have been followed over a period of some twenty-three years and not more than three of these patients have developed diabetes in later life.

A series of glucose tolerance tests on men in the Army are presented. These patients were investigated because of glycosuria. A series of non-diabetic glycosurias are presented to indicate some of the variations. These differ somewhat from a series one would encounter in civilian life, for soldiers largely represent a group of young men, approximately in the same age period (18-26 years). Whereas a civilian group would represent ages varying from extreme youth to eighty. In this second group one would naturally see a wide range in the height of renal threshold in contrast to the military group. Also, in the military group, the majority of the physically inadequate have been weeded out at induction. In the civilian group these would all be included and consequently one would not expect an identical picture of the renal threshold in the two groups.

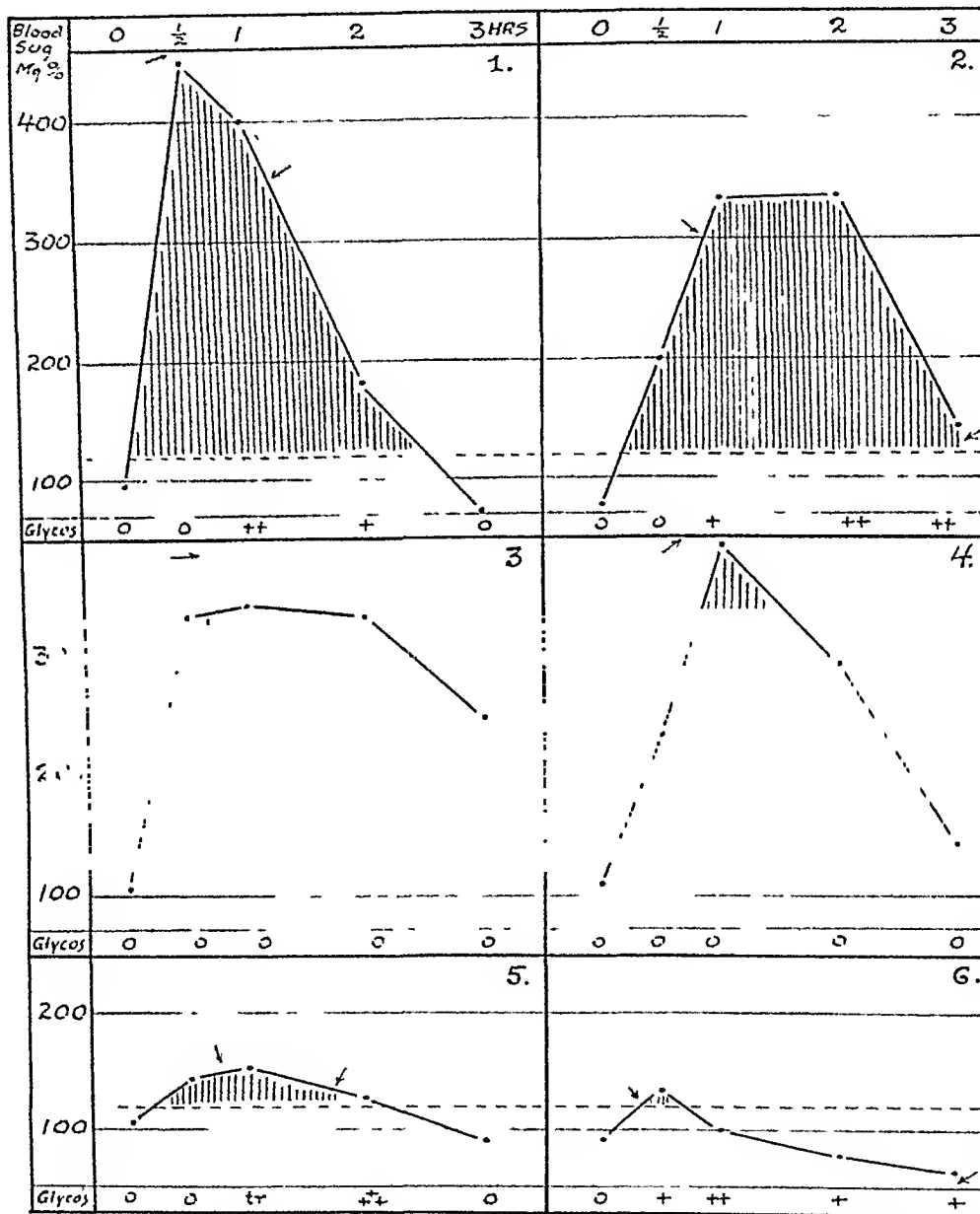
EXPLANATION OF CHARTS.

In the two charts presented, the curve of the individual glucose tolerance tests (57) are all done on the same scale. The scale for the blood sugar height is given at the left. The broken line, just above 100

indicates the upper level of normal blood sugar, 120 mg. per cent. The time element in the test is given at the top of the chart, in hours. The shaded portion of the chart indicates the length and the height of hyperglycemia. All tests were done with the standard dose of glucose, namely, 100 gm. by mouth on a fasting stomach. The arrows along the blood sugar curve in-

The first four curves in figure 1 represent early, mild diabetics, the so-called pre-diabetics. It should be noted that they all start with a normal blood sugar which points to a fallacy to which the author has called attention many times during the past twenty years; namely, the fallacy of doing a fasting blood sugar for the diagnosis of diabetes. It is worthless in the

FIG. 1



indicate the approximate level of renal threshold on the ascent of the curve as well as on its descent. It strikes one immediately that these two differ in nearly every case. On the ascent the threshold is invariably higher than it is on the descent. This is not a new observation, for nearly all workers in this field have called attention to this fact. It seems that it is more difficult for the sugar to get through the kidneys in the first place, but once the permeation of glucose starts, it continues through a lower level of blood sugar concentration. A satisfactory explanation for this phenomenon has not been made.

early cases of diabetes, and worse than useless as it is misleading. The two and a half hours post-prandial blood sugar would have given reliable information in all four instances, whereas, the fasting blood sugar would not have informed us of the patient's true status.

ABSTRACTS OF CASES:

Case 1. (Figure 1). A second lieutenant, thirty-four years of age. Admission diagnosis: Psychoneurosis, hysterical type. No diabetic history in the family. In 1924 he was hit with a baseball bat over the head, but there was no fracture. Again in 1935 he was hit with a baseball over the right eye and was unconscious for five or six hours. The GT (glucose tolerance)

was done as a routine test on the neuropsychiatric service. The curve is somewhat abnormal, the rise is quick in the first half hour at which time the blood sugar rose from 97 to 450 mg. per cent. The drop is also rapid, but note the length of hyperglycemia which in this case is two and a half hours. Such a case bears watching. This case is presented not because of the type of curve but to illustrate the possible height of the renal threshold (RT) for sugar. This is the highest threshold in the author's experience. Note that at 450 mg. per cent of blood sugar concentration, there is no glycosuria. On the curve's descent, however, we encounter glycosuria at 400. This would indicate that after the half hour estimation the blood sugar must have risen above 450, reached its RT value and once the permeation of sugar from the blood stream started, it continued. On the curve's descent it stops somewhere around 360 mg. per cent (note the arrow).

Case 2. (Figure 1). A first lieutenant, thirty-one years of age. Admission diagnosis: Encephalopathy. His main complaint was headaches. No history of diabetes in the family. He was in an automobile accident five months previously and received a cut on the right side of the head. He was back on duty in two weeks but began complaining of headaches. The GT was done as a routine procedure on the neuropsychiatric service. Note that the curve starts with a normal fasting BS (blood sugar). The curve is not as high as the one in case 1, but it is more prolonged which is of greater importance. At the end of the third hour the BS is still above normal. This curve (as all of the first four curves) is presented to illustrate the renal threshold. In this case it is around 300 on the ascent and somewhat around 120 mg. per cent on the descent.

Case 3. (Figure 1). A first lieutenant, fifty-six years old. Admission diagnosis: Diabetes mellitus, arteriosclerosis, varicose veins. His father died of diabetes and the patient has had diabetes for the past twenty-four years. (In spite of the length of his diabetes he turned out to be a mild diabetic and was discharged on a slightly restricted diet without insulin, as his blood sugar ranged from 100-118-105, morning, noon and night, before meals). It is noteworthy that though a diabetic for twenty-four years his fasting BS is normal. The curve is definitely of a diabetic type, for, had the observation been carried out further, it is clear that it would take some four and a half to five hours for the curve to return to normal. His RT is high, for, while the BS reaches 364 there is no glycosuria and none through the test. We must consider, therefore, that the threshold lies somewhere above 364 mg. per cent. Such a diabetic would be hard to evaluate on urine examinations alone or on fasting blood sugar values.

Case 4. (Figure 1). A soldier, private, twenty-eight years of age. Admission diagnosis: Dementia praecox, simple. The test was done as a routine procedure on the neuropsychiatric service. It was noted, however, that in addition to the above diagnosis the patient was jaundiced and had an icteric index of 100 at the time of the test. This introduces another factor into the test, namely, hepatitis, which does not concern us here. (When the test was repeated a month later after the jaundice subsided, the test was normal). We are primarily interested here with the renal threshold which is somewhere above 396 mg. per cent; no glycosuria occurred throughout the test.

Case 5. (Figure 1). A first lieutenant forty-six years of age. Admission diagnosis: Pancreatitis, non-suppurative, subacute, severe. He had been well until eight days prior to admission but had showed glycosuria regularly for seven days before admission. A fasting of BS was done which was 90 mg. per cent. A month after his admission a GT was done at a time when all symptoms had subsided. Note the slight rise of the BS throughout the test and the low RT, slightly higher on the ascent, than on descent. From the configuration of the curve it is clear that we are dealing with a case of non-diabetic glycosuria.

Case 6. (Figure 1.) A soldier, private, twenty-two years of

age. Admission diagnosis: Diabetes mellitus. His mother and one aunt are diabetic. He had been diagnosed and treated for diabetes by one of our leading medical institutions for the past ten years. When first seen, he was taking ten units of Protamine zinc insulin daily. The insulin was discontinued after preliminary blood sugar studies which were all normal before the three meals. He was followed for some time and three GT's were done during the thirty-nine days of observation. During this period all tests were normal. Note the GT curve. There is practically no rise in BS but there is an almost constant glycosuria. The RT is somewhere around 120 on the ascent and below 65 mg. per cent on the descent. Such a case needs no comment.

Case 7. (Figure 2). A major, forty-seven years old. Admission diagnosis: Nasopharyngitis, sinusitis, bronchitis, myocardial insufficiency with mild angina pectoris. There is no diabetes in the family. By occupation he was a general practitioner and a surgeon. The GT shows some hyperglycemia, but the curve returns to normal within two hours, and is, therefore, normal. RT on the ascent is somewhere around 132 and on descent around 120. The existing infection was probably a contributory factor in the height of BS but the elevated BS is of no significance.

Case 8. (Figure 2). A captain, thirty-four years old. Admission diagnosis: Dementia praecox, paranoid type. No diabetes in family. The test was done as a routine measure. Here we note the RT on the ascent above 222 whereas on the descent it is a little below 200 mg. per cent.

Case 9. (Figure 2). A soldier, private, twenty years old. Admission diagnosis: Heavy, repeated glycosuria. Tumor of anterior part of chest. There is no diabetes in the family. The GT is normal. RT on the ascent is somewhere around 180 and on the descent around 124 mg. per cent.

Case 10. (Figure 2). A soldier, private, twenty-seven years old. Admission diagnosis: Psychoneurosis. Two years before the present studies he had the following symptoms: Polyuria, polydipsia, glycosuria and weakness. He was told he had diabetes and was placed on a rigid diet and lost from 169 to 122 pounds. He was rejected twice for army service but on the third examination was inducted. The above history demanded further investigation and the GT shows the answer. There is no diabetes, simply a non-diabetic-glycosuria. The curve is extremely low and the RT on the ascent about 110 and on the descent below 78 mg. per cent. In spite of a good diabetic symptomatology, there is no diabetes present; a mere non-diabetic glycosuria.

Case 11. (Figure 2). A soldier, private, thirty years old. Admission diagnosis: Glycosuria. There is no diabetes in the family. He has had kidney stones in the past, two have been passed in the last three years. The GT is normal. RT on the ascent is somewhere around 170 and on descent around 130 mg. per cent. While at no time does the curve rise high, he is excreting sugar freely.

Case 12. (Figure 2). An applicant for induction, twenty-seven years old. He is supposed to have had diabetes for a year but has not taken any insulin. He was sent in for evaluation of his glycosuria. From the GT it is evident that the man was not a diabetic but had a low RT, below 99 on the ascent and slightly above 120 mg. per cent on the descent. Here we see a reversal of the RT from that seen in the other curves; a slightly higher value on the descent. At any rate diabetes was definitely ruled out and the case was a clear case of non-diabetic glycosuria.

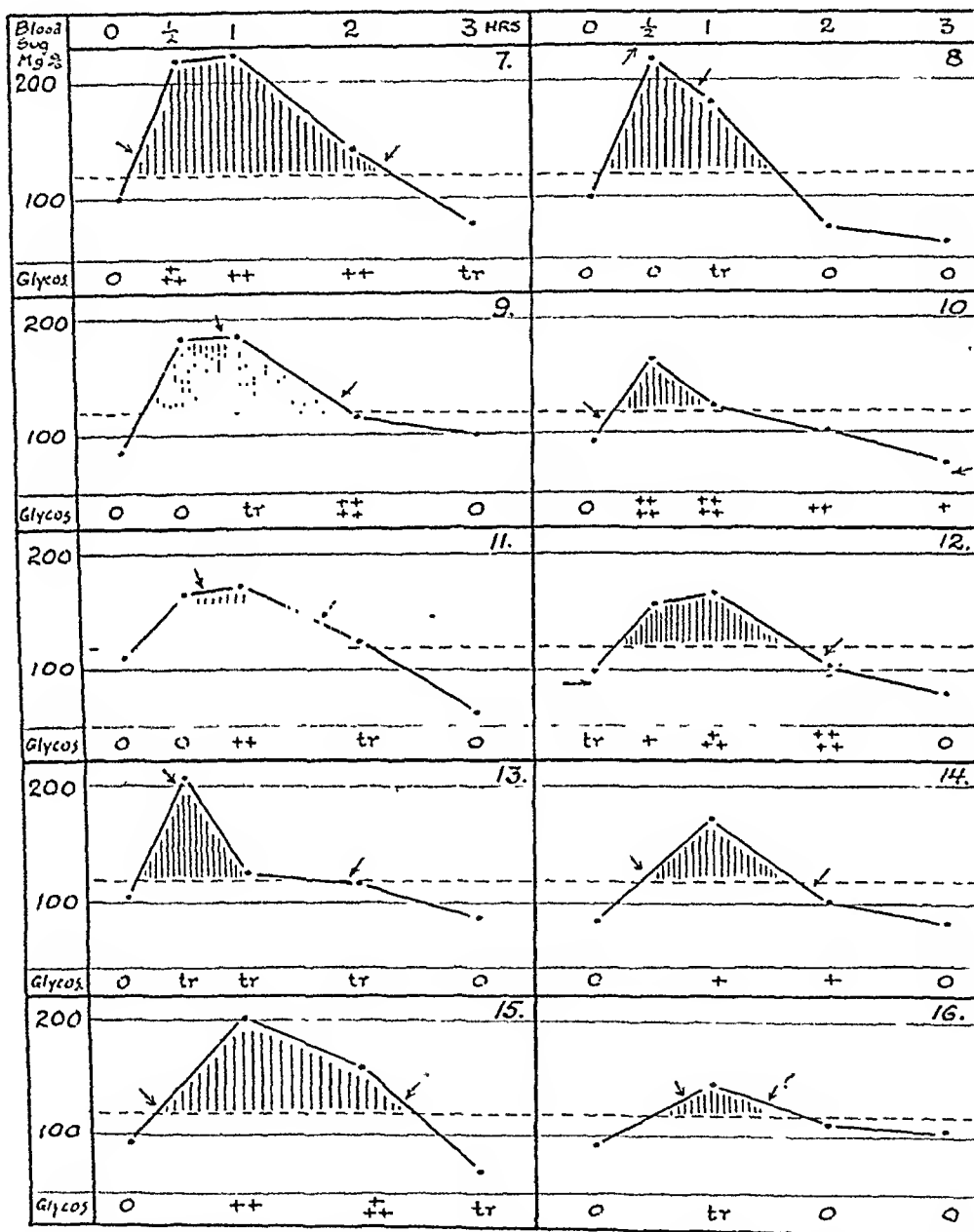
Case 13. (Figure 2). A soldier, private, twenty-six years of age. Admission diagnosis: Psychoneurosis, anxiety state, moderate. There is no history of diabetes in the family. He was told he had diabetes nine years previously and has been on a diet ever since without insulin. The GT is normal. RT on the ascent is around 200 and on the descent about 120 mg. per cent. This is a clear cut case of non-diabetic glycosuria.

Case 14. (Figure 2). A private, first class, twenty years old. Admission diagnosis Glycosuria. The glycosuria was found when he was examined for admission to the Air Corps. There is no diabetes in his family. He had pyelitis five months previously while in Panama. No symptoms of diabetes. The GT is perfectly normal. RT on the ascent around 126 and on the descent slightly below 120 mg. per cent. A clear cut case of non-diabetic glycosuria.

for the slight prolongation of the curve. Strictly speaking one would include him in the non-diabetic glycosuria group but he should be followed over a longer period.

Case 16. (Figure 2). A sergeant, thirty-five years old. Admission diagnosis: Glycosuria. No diabetes in the family. No symptoms of diabetes. He has been in service ten years. He had a chancre five years ago, but the serology is now

FIG. 2



Case 15. (Figure 2). A corporal, twenty-six years old. Admission diagnosis: Glycosuria. Maternal aunt has diabetes. The glycosuria was discovered a month before his admission to the hospital. The GT is slightly prolonged, it takes two and a half hours for the BS to reach a normal level, but this curve may still be included in the normal category. However, the patient needs further observation. (Repeated BS studies, tid a.c. were normal.) The RT on the ascent is slightly above 120 mg. per cent and on descent about the same level. Such a curve in a patient with his history, has to be interpreted with caution. He had been told he had diabetes so naturally he was careful of his diet. The GT was done only three days after placing him on a normal diet. The low carbohydrate food intake preceding the test could well account

negative. He was treated for diabetes on the basis of glycosuria and a GT which was supposed to have indicated diabetes. No data from the original test are available. Repeated BS studies, tid a.c., and repeated GT at this hospital were all normal, in fact very low. The RT is low, somewhere around 130 mg. per cent both on the ascent and descent. This test was done after he had been on a normal diet for some time. It is obvious that he is not a diabetic but shows glycosuria merely because of his low RT.

DISCUSSION

Now as one glances over the graphs of this group of sixteen cases, the outstanding difference in the

curves is that the first four curves are those of diabetics and have a high and prolonged hyperglycemia (the shaded portion) in contrast to the others. Here too, the renal threshold on the whole is high, very high in fact in all cases (Table 1). These are diabetic patients with little or no glycosuria.

The next twelve cases are all cases of non-diabetic glycosuria. Here the curves are low and the duration of the hyperglycemia (shaded portion) is short. This contrast is quite obvious. The RT in this group is on the whole low, quite in contrast to the first group of four cases. In this second group the differences between the RT on the ascent and the descent are less. We have, therefore, a more even distribution of glycosuria, through the whole period of the test. In some of these curves the RT is indeed very low, although not as low as in some cases observed in civilian life.

One must, therefore, be very careful in giving an opinion as to the significance of glycosuria. The only safe way is to do a GT, so that in the future the objective data on which the opinion was based are available for reference. One word of warning: be sure that the patient has not been on a starvation or freak diet preceding the test and that he does not have a severe infection. If a normal GT is obtained in spite of an infection or a previously abnormal diet, it may be accepted. However, if a mildly diabetic curve or even a frank diabetic curve is obtained it should not be accepted as final. Repeat the test later when the patient has been on a normal diet for at least a week or when his infection has cleared.

There is no treatment for a low renal threshold or non-diabetic glycosuria. The low threshold exists and will continue uninfluenced by therapy. There is no valid reason to attempt to change it. The actual amount of sugar lost in twenty-four hours in ninety-nine per cent of the cases is minimal, only a few grams. This loss does not affect the body economy and we can safely disregard it. There is no reason for dietary restrictions in patients unless some other condition, such as obesity, makes it desirable. A rational life and moderation in eating habits is all that is needed. More than this belongs in the category of "hoodooism".

One more point should be mentioned here. When glycosuria is found and the patient is subjected to repeated urinalysis and other examinations, he leaps to the conclusion that he has diabetes. He is apt, from fear, to restrict his diet markedly without the knowledge of the physician. Such a self-imposed diet may be very rigid, for fear will do queer things. Thus, when after repeated urine examinations, the two and a half hours post-prandial blood sugar test, or the glucose tolerance test is finally done, it is apt to give a high figure or misleading information. When a glucose tolerance test is done on a patient who has been on a rigid diet, the resultant curve may show a trend towards the diabetic type. If such a patient is put on a normal diet for a week and the test repeated, the second curve will be normal. This is a well known fact and should be borne in mind. All the investigations and tests should be done during the first twenty-four hours after glycosuria is discovered. This will

eliminate the possibility of introducing an extraneous factor with resulting unreliable findings and wrong interpretations.

There are minor exceptions to the statements made in the previous paragraphs, for other factors, known and unknown enter into the glucose tolerance test. If the general rules laid down in this article are followed, a high batting average of correct diagnoses will be attained. Some day an explanation may be found for the small group of other abnormalities occasionally encountered.

The glycosuria of pregnancy should be mentioned. Here the previously described rules again apply. A two and a half hours post-prandial blood sugar will indicate whether or not we are dealing with diabetes. If it is diabetes then immediate and proper care is indicated. Any glycosuria of pregnancy should be immediately investigated and a sound decision as to its significance reached. This is of vital importance to the patient and her physician. Glycosuria in this group should never be dismissed with the statement, "It is likely milk sugar". Lactosuria is never found in early or mid-pregnancy. It first occurs at the end of pregnancy and during lactation. Even if it is ascertained that the glycosuria is due to lactose in the urine, this does not eliminate the possibility of diabetes. Can not a diabetic woman who becomes pregnant, have lactose as well as glucose in the urine? This possibility may exist in the case at hand and it will NOT be settled by numerous and painstaking urine examinations. For a definite answer, a two and a half hours post-prandial blood sugar determination should be done. Why not do this immediately after the first positive urine test? Doubt and delay will then be eliminated.

TABLE I
Variation in the Renal Threshold in Ascent and Descent in 16 Patients

No	Age	Renal Threshold Mg. Per 100 Cubic Centimeters			Difference in milligrams
		Ascent	Descent		
1	34	450+	360		90
2	31	300	120		180
3	56	364+	364+		0
4	28	396+	396+		0
5	46	140	126		14
6	22	120	65		55
7	47	132	120		12
8	34	222+	200		22
9	20	180	124		56
10	27	110	78		32
11	30	170	130		40
12	27	99	120		21+
13	26	200	120		80
14	20	126	120		6
15	22	120	120		0
16	35	130	130		0

CONCLUSIONS

1. The differential diagnosis between diabetic and a non-diabetic glycosuria can be made only by a glucose tolerance test or by a blood sugar estimation two and a half hours following a heavy carbohydrate meal.
2. Numerous urine estimations for sugar for diagnostic purposes settle nothing and waste time.

3. Non-diabetic glycosuria is not a precursor of diabetes.

4. The renal threshold in a non-diabetic glycosuria is usually low. It varies on the ascent and descent of the curve, being higher on the former and lower on the latter.

5. Upon the finding of glycosuria, a diagnosis should be arrived at without delay (within twenty-four hours). This will eliminate the possibility of self-imposed dietary restrictions which distort the glucose tolerance curve (toward the diabetic side) and thus give false information.

6. There is no treatment for non-diabetic glycosuria and none is needed.

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Prevention of Gastric Ulcer Formation During the Alarm Reaction

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DURING the past few years it has been possible to show that the acute gastric ulcers, which occur in man as well as in animals following exposure to various noxious agents (*e.g.* toxic doses of drugs, cold, exhausting muscular work, surgical shock, etc.), are not due to any of the specific properties of these agents. They are apparently part of the response to the non-specific damage caused by these stimuli and merely represent one of the symptoms of the "alarm reaction" (1). The frequent occurrence of acute, often perforating, gastric ulcers in the population of heavily bombed areas (2-9) as well as in sailors and soldiers (10-12) exposed to continued physical or mental strain gave a certain timely practical importance to the problem of preventing or curing such lesions. The experiments which we wish to describe in this communication indicate that ulcers of this type may be prevented by the administration of various food substances, especially glucose, or by the neutralization of the gastric contents. In choosing these therapeutic agents we have been guided by previous observations which showed that traumatized tissues apparently consume more than the usual amount of glucose (13) and that fasted animals are especially sensitive to the gastric ulcer producing effect of alarming stimuli (1). Clinical observations support the view that in man fasting also enhances the formation of peptic ulcers (14-15). That neutralization of the gastric acid may be useful is almost self-evident since acidity promotes gastric digestion and hence would enhance the destruction of cells in the lining of the stomach.

EXPERIMENTAL

In order to test the prophylactic effect of various foods, dextrose and buffer solutions, we performed a

series of experiments in male and female rats. Our results are summarized in Table I. Only a few remarks will be necessary to elucidate the data given there:

Experiment 1: After first withdrawing food and water for 24 hrs., the animals in group "a" were allowed water and those in group "b" water and "purina fox chow" *ad lib*. Three hours later their spinal cord were cut at the height of the seventh cervical vertebra and both food and water were withdrawn from all animals. They were killed 16 hours after this intervention. In confirmation of our previous observations concerning the production of gastric ulcers by this surgical procedure we found, in addition to other symptoms of the alarm reaction (marked enlargement of the adrenal cortex, thymus atrophy, hemoconcentration, etc.), pronounced bleeding ulcers in the stomach of the fasted animals in group "a" but not in the fed animals of group "b". Since the extent of ulcer formation cannot readily be expressed in a precise quantitative manner a scale, ranging from 0 to ++++, has been established, and in the table the average values are registered for each group.

Experiment 2 and 3: After first withdrawing food and water for 24 hrs. all groups were given water *ad lib*, and all, excepting group "a" which acted as a control) received prophylactic treatment either by gavage or by ingestion. In the former case the substances were administered in several doses (see table I) through a stomach tube, while in the latter case, the substances were merely placed into the cages. Since the animals were fasted, they willingly took large amounts of these food substances so that their stomachs were filled at autopsy following conclusion of the experiment. The spinal cords of all animals were transected (as in experiment 1) two hours after the first administration of the various preventive agents

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and the water, as well as all food given *ad lib*, were withdrawn. Those animals receiving prophylactic treatment by gavage were given the last three doses during the 8 hrs. after the operation; then all animals were sacrificed. Perusal of the table indicates that in experiment 2 among the food substances, "purina," was definitely effective although unlike in the previous

Experiment 4 and 5: After first withdrawing food and water for 24 hrs. 33% dextrose was given intravenously or by gavage in two doses, one hour before and three hours after the spinal cord was cut. The animals were killed eight hours following this observation. It will be seen from the table that sugar administration was highly effective in preventing ulcer

TABLE I
Prevention of Gastric Ulcers during Alarm Reaction

Experiment			No. of Rats	Weight in g.	Damaging Agent	Preventive Agent		Amount	Stomach Ulcers
1	a		3 females	227 (210-242)	Spinal Cord transection	Water	ingestion	<i>ad lib.</i>	+++
	b		3 females	222 (200-242)	Spinal Cord transection	Purina	ingestion	<i>ad lib.</i>	0
2	a		2 males +	268 (245-300)	Spinal Cord transection	Water	ingestion	<i>ad lib.</i>	++
	b		2 females	261 (215-300)	Spinal Cord transection	Rice Starch	ingestion	<i>ad lib.</i>	++
	c		2 females	278 (220-370)	Spinal Cord transection	Casein	ingestion	<i>ad lib.</i>	++
	d		2 females	273 (220-340)	Spinal Cord transection	Lard	ingestion	<i>ad lib.</i>	++
	e		2 females	272 (250-300)	Spinal Cord transection	Purina	ingestion	<i>ad lib.</i>	+
	f		2 females	264 (205-340)	Spinal Cord transection	1% Na Bicarbonate	gavage	2 cc. x 5	++
	g		2 females	278 (223-320)	Spinal Cord transection	Amphojel*	gavage	2 cc. x 5	0
3	a		6 males	230 (185-355)	Spinal Cord transection	Water	ingestion	<i>ad lib.</i>	++
	b		6 males	226 (166-380)	Spinal Cord transection	33% Dextrose	gavage	2 cc. x 4	0
	c		6 males	238 (180-370)	Spinal Cord transection	Purina	ingestion	<i>ad lib.</i>	0
	d		5 males	217 (175-280)	Spinal Cord transection	Meat	ingestion	<i>ad lib.</i>	0
	e		6 males	231 (170-394)	Spinal Cord transection	1% Na Bicarbonate	gavage	2 cc. x 4	++
	f		6 males	216 (175-270)	Spinal Cord transection	Amphojel	gavage	2 cc. x 4	0
4	a		8 males	142 (120-155)	Spinal Cord transection	Water	gavage	3 cc. x 2	++
	b		4 males	148 (140-159)	Spinal Cord transection	33% Dextrose	i.v.	3 cc. x 2	0
	c		7 males	141 (128-152)	Spinal Cord transection	33% Dextrose	gavage	3 cc. x 2	0
5	a		8 males	136 (125-144)	Spinal Cord transection	Water	gavage	2 cc. x 2	++
	b		8 males	134 (125-145)	Spinal Cord transection	33% Dextrose	i.v.	2 cc. x 2	0
	c		8 males	135 (125-145)	Spinal Cord transection	33% Dextrose	gavage	2 cc. x 2	0
6	a		12 males	162 (120-220)	Cold	Water	gavage	2 cc. x 3	+++
	b		12 males	181 (125-220)	Cold	33% Dextrose	gavage	2 cc. x 3	0
	c		8 males	188 (165-210)	Cold	Amphojel	gavage	2 cc. x 3	0

* Aluminum hydroxide in the form of a colloidal gel, prepared by John Wyeth & Brother (Canada) Ltd.

experiment it did not prevent ulcer formation completely. Among the buffer solutions, amphojel was highly effective while sodium bicarbonate had no effect although the gastric contents were neutral to litmus paper at the time of autopsy. In Experiment 3, amphojel and all food substances proved highly effective but sodium bicarbonate was again without beneficial action.

formation and that this effect was obtained not only when the dextrose was placed in immediate contact with the gastric surface, but even when it was administered through the general circulation.

Experiment 6: In order to determine whether ulcers produced by stimuli other than spinal cord transection could be inhibited by dextrose, an additional experi-

ment was carried out in which the damaging agent was exposure to low temperature. Food and water were withdrawn for 48 hrs. before this experiment, since previous observations showed that especially severe gastric ulcers will occur under the influence of exposure to low temperatures following a prolonged fast. After this the rats were placed into a refrigerated room at a temperature of $+6^{\circ}\text{C}$. Their fur was clipped short and kept wet by repeated immersion into water in order to make the animals lose heat rapidly. Dextrose or amphojel were administered just before placing the animals in the cold room and twice after that. They were sacrificed following 8 hours of exposure to cold. It will be seen that here again dextrose proved just as efficient as amphojel in preventing ulcers.

experimental procedure the following facts should be pointed out:

Experiment 1: Food and water were withdrawn from the animals at the time of the first subcutaneous formaldehyde injection. After this both the formaldehyde and the dextrose were given at intervals over a period of 53 hours after which all rats were killed.

Experiment 2: Food and water were withdrawn from all animals for 48 hours after which time the rats in group "c" were given their first dose of dextrose and the controls in group "a" and "b" their first dose of water. One hour later the spinal cords of the rats in groups "b" and "c" were transected, (again at the height of the 7th cervical vertebra). The other two doses of dextrose and water respectively were ad-

TABLE II

Blood Sugar variations accompanying prevention of Gastric Ulcers during Alarm Reaction

Experiment			No. of Rats	Weight in g.	Damaging Agent	Preventive Agent		Amount	Stomach Ulcers	Blood Sugar
1	a		6 males	102 (90-115)	---	Water	gavage	2cc x 13	0	63.8
	b		6 males	105 (90-125)	2cc 10% Formaldehyde x 14 s.c.	Water	gavage	2cc x 13	+	83.2
	c		6 males	99 (90-120)	2cc 10% Formaldehyde x 14 s.c.	33% Dextrose	gavage	2cc x 13	0	608.2
2	a		6 males	102 (85-115)	---	Water	gavage	2cc x 3	0	57.8
	b		5 males	107 (95-115)	Spinal Cord Transection	Water	gavage	2cc x 3	+++	53.2
	c		5 males	98 (85-115)	Spinal Cord Transection	33% Dextrose	gavage	2cc x 3	0	*
3	a		6 males	122 (105-130)	---	Water	gavage	2cc x 3	0	45
	b		6 males	115 (95-130)	Cold	Water	gavage	2cc x 3	+++	30
	c		6 males	123 (115-130)	Cold	33% Dextrose	gavage	2cc x 3	0	80

* Samples Lost.

Summarizing this part of our work, it may be said that the gastric ulcers, which appear during an alarm reaction elicited by transection of the spinal cord or exposure to cold, are effectively prevented by the administration of various food substances, especially dextrose, and that this latter compound is beneficial, whether administered orally or by intravenous injection. Among the buffer substances, amphojel proved effective but sodium bicarbonate exerted no detectable beneficial action.

In view of the beneficial action exerted by glucose administration, it appeared of some interest to elucidate the possible role hypoglycemia might play in the pathogenesis of acute gastric ulcers. For this purpose three additional series of experiments were performed. Two again with spinal cord transection and exposure to cold and a third with a new "alarming agent" namely formaldehyde. The results of these experiments are summarized in table 2. Concerning the details of the

ministered at intervals until 7 hours after operation, when the animals were killed.

Experiment 3: Food and water were withdrawn from all animals for 48 hours and at the end of this time the rats in groups "b" and "c" were placed in a refrigerated room at a temperature of $+2^{\circ}\text{C}$ for 9 hours at the end of which time they were killed.

In all three experimental series blood was collected from the jugular vein and its glucose content was determined by the Somogyi-Shaffer and Hartmann method (16).

Perusal of table 2 clearly indicates that, irrespective of the type of alarming agent used, dextrose is highly effective in preventing the acute gastric ulcers characteristic of the alarm reaction. Hypoglycemia does not appear to be the primary cause of the gastric ulcers since the blood sugar of groups "b" did not fall significantly below that of groups "a" in any of these experiments. Furthermore perusal of the individual



Figure 1—On the left, gastric mucosa of a rat from experiment 3; group "a", showing gastric ulcers produced by spinal cord transection. On the right, gastric mucosa of a similarly treated rat from group "b" in which ulcer formation was completely prevented by dextrose treatment.

blood sugar values shows a great deal of overlap between groups "a" and "b" although marked gastric ulcers were obvious in all individuals of group "b" and in none of group "c". It will be noted, furthermore, that in experiment 3 the dextrose treatment prevented the formation of gastric ulcers although the dosage was too low to raise the blood sugar throughout the duration of the experiment.

SUMMARY

Experiments in albino rats indicate that the gastric ulcers which appear in the course of a severe alarm reaction (produced by high spinal cord transection) may be prevented by the prophylactic administration of various food substances, aluminum hydroxide gel and especially by comparatively small doses of dextrose.

Dextrose is effective when given either per os or intravenously. It prevents gastric ulcer formation even in doses insufficient to raise the glucose content of the blood above the normal level for the duration of the experiment. The prophylactic effect of dextrose is non-specific in the sense that the compound prevents the formation of gastric ulcers by a variety of widely different damaging agents such as formaldehyde injections, exposure to cold or spinal cord transection.

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Salmonella Enterocolitis in Infants and Children

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AMONG the microorganisms responsible for diarrheal disease in infants and children the paratyphoid bacilli or the members of the genus *Salmonella* figure much more prominently than is generally believed. Many questions pertaining to diagnosis, mode of transmission, and therapy of this infection remain unanswered. The state of the *Salmonella* problem was presented recently in an excellent review by Bornstein (1). During 1943, at the Children's Hospital, 21 bacteriologically proven cases of *Salmonella* enterocolitis were studied. During that period other paratyphoid infections, such as paratyphoid fever, *Salmonella* meningitis and septicemia were observed. The following report is concerned with various bacteriological, and clinical aspects of enteritis, colitis, and enterocolitis caused by *Salmonella* organisms in infants and children.

Eleven cases of diarrheal disease were caused by *S. typhi* murium. The pertinent data with respect to age, sex, and race of the patient, bacteriological findings, chemotherapy, and outcome are summarized in Table I. Interesting is the fact that none of these patients was older than a year and a half and that stool cultures were taken routinely on all patients with diarrheal disease, irrespective of age. All eleven patients were admitted to the hospital during the months of January to May; no other case of *S. typhi* murium infection was seen during the remaining months. Although some of the patients undoubtedly were suffering from the infection at the time of admission, others developed enterocolitis during their stay at the hospital. One patient, J. B., was admitted because of erysipelas and an upper respiratory infection on May 16, 1943. Three days later a stool culture revealed the presence of *S. typhi* murium and on May 21 the child developed diarrhea. Another patient, P. K., developed *S. typhi* murium enterocolitis during convalescence from meningococcal meningitis. A third patient, L. B., was admitted to the hospital suffering from eczema and was free from diarrhea from March 23 to April 5, 1943. The day after discharge the patient developed diarrhea and was readmitted because of this condition on April 7. Subsequently, both stool and blood cultures became positive for *S. typhi* murium and the patient died on April 25. In attempting to discover the source of these infections the possibility was considered that they may have originated either from

cases suffering from *S. typhi* murium enterocolitis or from carriers among those persons attending, or in direct contact with the patients. As far as could be determined there was no instance of diarrhea among the attendants of this hospital and stool cultures failed to reveal *S. typhi* murium. One of the patients, C. G., suffering from enterocolitis was born at another hospital and bacteriological studies on the mother and nursing staff could not be carried out. Thus, attempts to trace the direct origin of these infections were unsuccessful.

Nine of the 11 patients were treated with sulfonamide compounds, namely, sulfanilamide, sulfathiazole, sulfadiazine, and sulfasuccidine. Two succumbed to the infection and 9 recovered. One of the fatal cases, L. B., suffered from *S. typhi* murium bacteremia and enterocolitis; in the other case, C. G., a blood culture was not taken. Whether or not chemotherapy contributed to the recovery of the other patients cannot be stated. It should be mentioned, however, that sulfonamides failed to eradicate the organisms from the intestinal tract in some of these cases. One patient, for instance, was treated with sulfasuccidine from June 3 to June 15; *S. typhi* murium was recovered from the stools twice during that period and 6 times thereafter. Another patient received the same drug from March 13 to May 17. During that period 6 out of 8 stool cultures were positive for *S. typhi* murium.

The second group is comprised of 10 cases of enterocolitis caused by *Salmonella* organisms other than *S. typhi* murium. The pertinent data are summarized in Table 2. The patients ranged in age from 3 weeks to 12 years. Stool cultures were positive for *Salmonella* organisms in all instances. Blood cultures were taken in 4 cases and were found to be negative for this organism. One case of this group is of particular interest. This patient, R. D., suffered from beta hemolytic streptococcal bacteremia and *Salmonella* enterocolitis. The paratyphoid bacillus was recovered from the stool of this patient while convalescing from septicemia.

Five patients from this group were treated chemotherapeutically with sulfathiazole, sulfadiazine, and sulfasuccidine. Nine of the patients recovered from the infection and one child died. The latter was a baby, H. G., 5½ weeks old, who was not treated with sulfonamides.

The patients presented in this group were seen between January and September, 1943; two in January, one in February, three in March, one in May, two in June, two in August, and one in September. In contrast to the *S. typhi* murium infections, these cases

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were more or less evenly distributed during 9 months of 1943.

DISCUSSION

During 1943 at the Children's Hospital, 21 cases of enterocolitis in infants and children, apparently caused by paratyphoid bacilli, were studied. The diagnosis of *Salmonella enterocolitis* is based upon the presence of paratyphoid bacilli in the intestinal tract of these patients. No other pathogenic microorganisms were found. Moreover, in one instance paratyphoid bacilli were also recovered from the blood stream. It should be borne in mind, that, while the presence of enteric pathogens in the feces does not necessarily indicate that they are the cause of actual inflammatory changes, the evidence at hand supports the supposition that the *Salmonella* organisms were important factors in the development of the diarrheal disease of the cases presented here.

Of the 21 patients, 18 were less than two years and 10 less than 3 months of age. The youngest child reported here was 11 days old at the onset of the illness. Mention should be made that stool cultures were taken in all cases of diarrheal disease irrespective of age. Thus, the conclusion is warranted that either infants

In several instances *Salmonella enterocolitis* developed in infants and children suffering or recuperating from other illnesses, namely, meningococcal meningitis, beta streptococcal bacteremia, and bronchopneumonia. A similar observation was reported (Harvey (4), Neter (5)) in *S. choleraesuis* infections following pneumonia, gonococcal urethritis, streptococcal pharyngitis, scarlet fever, rheumatic heart disease, and surgical procedures. Ravitch and Washington (6) described a case of meningococcal meningitis complicated by *Salmonella* bacteremia and meningitis. It is difficult to ascertain whether these primary infections rendered the patient more susceptible to *Salmonella* infection.

Among the 21 cases of *Salmonella enterocolitis* reported here, one was due to *S. thompson*. This case, J. S., seems to represent a rather unusual instance of infection by this species. Several members of the patient's family developed diarrheal disease and vomiting at the same time. Bacteriological examination and agglutination tests on these persons, however, failed to reveal evidence of *Salmonella* infection.

Eleven cases of enterocolitis were caused by *S. typhi*

Table I
Salmonella typhi murium enterocolitis

Name	Age	Sex	Race	Blood Culture	Stool Culture	Chemotherapy	Outcome
G. B.	1 month	Male	Negro	...	+	sulfathiazole sulfasuccidine	Improved
H. McC.	3 months	Female	White	...	+	sulfasuccidine	Improved
D. M.	3 months	Male	Negro	—	+	sulfasuccidine	Improved
R. G.	2½ months	Male	White	...	+	...	Improved
C. G.	11 days	Female	White	..	+	...	Died
P. K.	2 months	Female	White	..	+	sulfadiazine sulfasuccidine	Improved
C. D.	5 months	Male	White	...	+	sulfasuccidine	Improved
J. D.	7 months	Male	White	...	+	sulfanilamide	Improved
F. F.	1½ years	Male	White	..	+	sulfathiazole sulfasuccidine	Improved
L. B.	5 months	Male	White	+	+	sulfathiazole	Died
R. B.	6 months	Male	White	...	+	sulfasuccidine	Improved

+ : Positive for *Salmonella*

— : Negative for *Salmonella*

and young children are more susceptible to the infection or that the disease is more severe, requiring hospitalization. This observation parallels that of Seligmann, Saphra, and Wassermann (2) who recently reviewed 1000 cases of *Salmonella* infections in man. Of these 112 occurred in infants, 132 in children and 317 in adults. No data were available in the remaining cases. From an extensive investigation into the causes of infantile summer diarrhea, the Uruguayan investigators, Hormacche, Surraco, Peluffo, and Aleppo (3) drew the conclusion that "the occurrence of *Shigella* and *Salmonella* as causative agents in infantile enteritis is in inverse proportion to age, a proof that children are more susceptible to infection with these organisms than adults." Further studies seem to be indicated to determine the relationship between age of patient and relative susceptibility to *Salmonella* infection, particularly diarrheal disease, and the reasons for the variance in resistance and susceptibility.

murium. An analysis of this group of patients revealed that several children were admitted to this hospital for the diarrheal disease, whereas others developed enterocolitis at the hospital while undergoing treatment for reasons other than enteric disorder. All cases of *S. typhi murium* enterocolitis occurred during the first five months of 1943. The fact that the small outbreak of this infection came under control can probably be attributed to the improvement in technique and the added precautions employed by both physicians and nurses. It is not difficult to visualize the potential dangers of such infections, particularly when one bears in mind the added difficulties encountered in overcrowded hospitals during war-time. Infants and children should be protected as far as possible not only against respiratory but also against enteric infections. Attempts to trace the infection to a carrier attending these patients were unsuccessful.

Chemotherapy was employed in 14 out of 21 cases

The drugs used were sulfanilamide, sulfathiazole, sulfadiazine, and sulfasuccidine. No definite statement can be made regarding possible beneficial effects resulting from this treatment. Two of the fatal cases did not receive sulfonamides and the other was treated with sulfathiazole. It should be mentioned that in several instances chemotherapy with sulfonamides, including the use of sulfasuccidine, failed to eradicate the paratyphoid bacilli from the intestinal tract.

(4) Added precautions for the prevention of the spread of the infection contributed to the eventual check of the outbreak.

(5) In several cases *Salmonella enterocolitis* developed during or following other diseases, namely meningococcal meningitis, streptococcal bacteremia, and bronchopneumonia.

(6) Of the entire series 18 patients recovered and 3 died.

Table 2

Salmonella enterocolitis due to types other than S. typhi murium

Name	Age	Sex	Race	Blood Culture	Stool Culture	Chemotherapy	Outcome
E. S.	7 months	Male	White	—	+	sulfathiazole	Improved
M. S.	11 years	Male	White	—	+	sulfasuccidine	Improved
R. F.	2½ years	Male	White	...	+	sulfathiazole	Improved
						sulfadiazine	
						sulfasuccidine	
H. G.	5½ weeks	Male	White	—	+	...	Died
J. J.	3 weeks	Male	White	...	+	...	Improved
J. L.	1 year	Female	White	...	+	...	Improved
B. C.	4½ months	Male	Negro	...	+	sulfasuccidine	Improved
S. D.	2 months	Male	White	...	+	...	Improved
R. D.	3 years	Male	White	—	+	sulfadiazine	Improved
J. S.	12 years	Female	Negro	...	+	...	Improved

+ : Positive for *Salmonella*

— : Negative for *Salmonella*

SUMMARY

(1) Twenty-one cases of *Salmonella enterocolitis* in infants and children have been presented. The age of the patients ranged from 11 days to 12 years. Eighteen were less than 2 years, and 10 less than 3 months of age.

(2) One of these cases represents an unusual instance of *S. thompson enterocolitis*.

(3) Eleven cases of enterocolitis were due to *S. typhi murium*. Several of these patients were admitted because of this condition while others developed the diarrheal disorder during hospitalization for unrelated illnesses.

(7) Of the 21 patients 14 were treated with sulfonamides, namely sulfanilamide, sulfathiazole, sulfadiazine, and sulfasuccidine. One of the fatal cases was treated with this form of chemotherapy.

(8) The importance of paratyphoid bacilli as incitants of diarrheal disease in infants and children is stressed and the necessity for the prevention of such infections, particularly under war-time conditions, is emphasized.

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The Role of the Fat Soluble Vitamins A and D in Nutrition

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REQUIREMENTS OF VITAMIN D

AN IMPORTANT FACT is that vitamin D may be stored in the body to a considerable degree. It is thus possible to build up a reserve of this vitamin in the organism to be drawn upon during periods of depletion or deficient intake. Thus the vitamin D storage in the mother if in sufficient amount will give rise to an adequate supply in the tissues of the infant during prenatal development. Also ample reserves of the vitamin increase the potency of this substance in the milk. The bony structure of the newborn infant is therefore affected in two ways as a result of the building up of excessive amounts in the mother, first by actual storage in the tissues of the infant and secondly by continuing to supply the vitamin in its source of nourishment from the mother's milk.

The importance of proper vitamin D therapy for the pregnant mother, in so far as this may influence the development of rickets in the newborn is well shown in the report of Maxwell (*Maxwell, J. P. Osteomalacia and Foetal Rickets. Brit. J. Radiol. 3:375, 1930*). In one case of a mother suffering from osteomalacia, the newborn infant showed classical evidence of rickets. Similarly Wolfe (*Wolfe, J. J. Teeth in Fetal Rickets. Am. J. Dis. Child. 49: 905, 1935*) has shown the importance of the affect of the mother in the development of rickets in the newborn.

Obviously the prevention and treatment of infantile rickets should begin with the ample administration of vitamin D to the childbearing mother throughout the entire period of pregnancy. Of considerable importance is the fact Wolfe noted that although the skeletal changes in the newborn infant could be favorably influenced by the later administration of ample quantities of vitamin D, changes in the teeth remained as permanent evidence of the prenatal rickets.

During lactation, an ample supply of vitamin D is also of considerable importance to the mother, because among other reasons there is an increased excretion of calcium in the breast milk. The daily administration of about three hundred to four hundred International Units of vitamin D is therefore of considerable value to the adult, not only under ordinary conditions but particularly during periods of pregnancy and lactation.

The vitamin D requirements are important in infancy, not only for the maintenance of the normal tissues and particularly of the skeletal structure but also for the demands due to growth. It is important, therefore, not only for the avoidance of rickets but also to encourage and make possible superior growth. Thus Jeans and Stearns (*Jeans, P. C. and Stearns, G. The*

Human Requirement of Vitamin D. Chapt. XXVI The Vitamins, J. A. M. A. 1939) have shown that when the amount of vitamin D is liberal, it actually encourages the rate of growth, apparently by increasing the assimilability of calcium from the food intake.

The liberal administration of vitamin D is also a factor of safety during childhood. While increasing amounts of vitamin D were ineffective, in those children in whom a sufficient degree of calcium utilization was already present, it aided materially in encouraging such utilization in those children in whom this process was deficient. Ample vitamin D above that necessary for minimal needs is therefore a factor of importance for the nutritional welfare of children.

A survey of all the evidence indicates that an intake of between 300 to 400 units of vitamin D a day is sufficient not only to prevent the development of rickets but also for normal structural growth of the skeleton and teeth. The maximum influence on growth is obtained with amounts of vitamin D varying between 300 to 600 units a day.

Toxicity of Vitamin D

While the value of vitamin D in the metabolic processes of the organism is obviously unquestioned, its administration in very excessive amounts may prove to be toxic to the organism. In the experimental animal such hypervitaminosis may lead to serious derangements, such as vomiting, diarrhea, weight loss and an increase in the calcium content of the serum, leading to calcification of the blood vessels, stomach, kidneys, heart, lungs and bronchii. The quantity of vitamin D however necessary to produce toxic symptoms in man is very high and is estimated at a continuous daily dose of about 20,000 International Units per kilogram of body weight.

The safety in the administration of even large doses of vitamin D, however, is demonstrated by Reed (*Reed, C. I. Symptoms of Vitamin D Overdosage in Human Subjects. J. A. M. A. 102:1745, 1934*). He showed that there was little to be feared from the administration of amounts as high as 150,000 International Units a day for indefinite periods of time. Even when as much as 2,760,000 International Units of vitamin D, representing 920 times the ordinary antirachitic dose of 3,000 units, was administered, evidence of toxicity appeared in a comparatively small percentage of cases. Obviously then there is nothing to be feared from the usual procedure in the administration of vitamin D in the treatment of rickets.

Park (*Park, E. A. The Use of Vitamin D Preparations in the Prevention and Treatment of Disease. J. A. M. A. 111:179, 1938*) has stated the problem of the toxicity from excessive doses of vitamin D as follows:

* Continued from September Issue

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"The physician should be on his guard for signs of toxicity in the child if the daily dose exceeds 50,000 units. If the patient is a very small infant, e.g., a premature infant, the physician should watch with care even if the dose is 20,000 or 30,000 units. The toxic manifestations will not occur immediately but only after a period of two or three weeks and need not be expected so long as the rickets, if this condition is present, remains unaffected. With the adult the physician ought to exercise great caution in venturing into the unknown with daily doses of 200,000 units or more."

How really excessive such an amount is, can be seen from a determination of the amount required during health. Thus in the case of the infant and adolescent, the necessary quantity of vitamin D per day is 300 to 400 International Units. In the presence of established rickets, a somewhat larger amount of vitamin D is usually administered, up to 1500 International Units per day.

Further evidence of the fact that comparatively large doses of vitamin D may be administered without danger is shown by the work of Warkany, Guest and Grabill (Warkany, J., Guest, G. M., and Grabill, F. J. *Estimation of Vitamin D in Blood Serum: Vitamin D in Human Serum During and After Periods of Ingestion of Large Doses of Vitamin D*, *J. Lab. and Clin. Med.*, 27:557-565, Jan., 1942). They administered as much as 400,000 to 500,000 units of vitamin D per day, following which the concentration of the vitamin in the serum rose to between 9,000 and 13,000 I. U. per hundred cc., an amount equivalent to the antirachitic potency of cod liver oil. In spite of the large doses of vitamin D administered there were only few toxic symptoms.

The importance of a liberal intake of vitamin D has been shown by Albright, Butler and Bloomberg (Albright, Fuller; Butler, A. M., and Bloomberg, Esther: *Rickets Resistant to Vitamin D Therapy*, *Am. J. Dis. Child.*, 54:529, Sept., 1937). They noted that certain patients even in the absence of factors such as steatorrhea which interfere with the absorption of vitamin D, may develop rickets when an amount of vitamin D is included in the diet ordinarily sufficient to prevent the disease. In the particular case which they describe after the intravenous administration of ordinarily ample doses, a boy of sixteen, who had had rickets since the age of one, the condition resisted healing even amounts of crystalline vitamin D. When however, the amount of vitamin D given by mouth was massive such as doses ranging from 150,000 to 1,500,000 U. S. P. units per day, the cure of the disease was accomplished. In the majority of cases of refractory rickets, however, 50,000 to 60,000 units will be required to induce healing.

There are other cases which may require the administration of unusually large doses of vitamin D. Such a situation arises in cases of "thoracic rickets." Very rapid healing may be essential in order to save the life of the child and doses of 50,000 units of vitamin D per day have been recommended for this condition in early infancy, with a reduction in the amount as radio-

logic evidence of healing becomes demonstrable. All this of course presupposes that the diet itself contains liberal amounts of calcium and phosphorus.

Considerable caution should be exercised however, when massive doses of vitamin D are administered and the amount reduced at the earliest possible moment, consistent with clinical improvement of the patient, in order to avoid the onset of toxic manifestations.

Although there is less variability in the retention of calcium in infants fed with human milk than in the case of infants fed on cow's milk, the addition of vitamin D is of value in both the breast fed and artificially fed infant in insuring against the development of rickets.

In the prematurely born, the amount of vitamin D necessary to prevent rickets may be twice that essential in the case of the full term infant. The amount of vitamin D for the prematurely born infant should therefore be from 600 to 800 units per day.

Vitamin D and Infantile Tetany

Just as valuable as vitamin D is in the treatment of rickets so it is of equal importance in the therapy of infantile tetany. In the early stages of the treatment of this latter disease, calcium itself must be administered in fairly large amounts in addition to vitamin D. This is due to the fact that during the first few days of vitamin D administration, there is an occasional tendency for a diminution of the serum calcium which may actually cause an exacerbation of the disease. By combining calcium as in the form of calcium chloride with the vitamin D, such a possibility may be completely avoided. At the end of a week or ten days, the added calcium may be eliminated and the therapy depend on the continued administration of vitamin D.

Vitamin D and Osteomalacia and Osteoporosis

In addition to the importance of vitamin D to rickets, is its relation to osteomalacia which has an essentially similar pathogenesis. Thus the relation of vitamin D to the retention of calcium and phosphorus in osteomalacia is fundamentally like that in rickets, and the disease may therefore justifiably be considered as a form of adult rickets.

Osteoporosis is similarly a deficiency disease having some of the histologic characteristics of rickets, and amenable to favorable response following the administration of fish liver oil.

Vitamin D and Other Disorders

Although definite proof is lacking, vitamin D in large amounts has been recommended as being of value in the treatment of chronic arthritis (Vrtiak, E. G., and Lang, R. S. *Observations on the Treatment of Chronic Arthritis with Vitamin D*, *J. A. M. A.* 106:1162, April 4, 1936). Twenty cases of chronic atrophic arthritis were treated with daily doses of 150,000 to 250,000 U. S. P. units of vitamin D. Twelve of the patients (60%) showed varied degrees of improvement.

Based on the observation that ultraviolet irradiation in sufficient amount may produce a favorable effect on

the psoriatic lesion, Ceder and Zon (*Ceder, E. T., and Zon, Leo: Treatment of Psoriasis with Massive Doses of Crystalline Vitamin D and Irradiated Ergosterol; A Preliminary Report. Pub. Health Rep. 52:1580, Nov. 5, 1937*) carried out treatment on individuals suffering from psoriasis by means of the administration of massive doses of vitamin D. They had noted in treating cases of chronic arthritis with doses of vitamin D averaging 300,000 units per day that an individual with psoriasis showed complete disappearance of the lesion. They therefore applied this form of therapy to fifteen cases of chronic widespread psoriasis. Eleven of the patients showed a complete disappearance of the lesion within twelve weeks. Two others showed partial improvement while in two cases the lesion resisted the treatment.

Because of the enormous importance of vitamin D, the inclusion of some preparation of this vitamin should be universal. Not only is it of great value in infancy and childhood but even among adults its inclusion would be an aid in maintaining an optimal state of nutrition particularly during the less sunny periods of the year and for those whose work confines them mainly to indoors and shuts them off for a considerable period of the day from the beneficent rays of the sun. Among the aged also inclusion of vitamin D may be important, particularly if their digestion is poor or they are mainly confined indoors.

The value of vitamin D for the pregnant and nursing mother has been emphasized.

The Therapeutic Value of Fish Liver Oil as a Source of Vitamin D

The therapeutic effectiveness of fish liver oil in the cure of rickets had been particularly well shown by Pappenheimer in 1922 (*Pappenheimer, A. M. Experimental Rickets in Rats. J. Exper. Med. 36:335, 1922*). Evidence of the deposit of calcium in the cartilage as an indication of the curative effect of the fish liver oil could frequently be determined within the brief period of twenty-four hours. Within a period of forty-eight hours there is evidence of capillary invasion of degenerate cartilage and the development of bone trabeculae.

Park showed that halibut liver oil is not only much richer in vitamin A than cod liver oil but is also several times more potent in vitamin D as well. The vitamin A content of halibut liver oil, U. S. P. XII is a minimum of 60,000 units per gram. Not only therefore is halibut liver oil an excellent source of both vitamin A and vitamin D but gram for gram it is enormously more potent than cod liver oil as a source of vitamin A.

The amount of vitamin D in fish liver oils varies with the species. It also shows variation, depending on the season of the year, the climate and the food supply of the fish. In the case of the halibut, the oil of the liver is greater in quantity during the summer, but the potency as far as vitamin D is concerned is low. During the winter, however, there is less oil in the liver but it is relatively richer in vitamin D content.

Those sources which combine ample amounts of vitamin A as well as vitamin D are quite obviously of superior value. The concentrated fish liver oils which are excellent sources of both these fat soluble vitamins are therefore of superior value and are to be preferred to materials which include only one or the other of these essential food factors. Moreover, the fish liver oils may be used to fortify the vitamin A and D of milk and such a preparation will be superior to irradiated milk in its richness of vitamin A and D content.

Even when milk fortified with vitamin D is administered, the liberal addition of the highly concentrated fish liver oils may prove to be of value in the prevention of rickets in infancy and particularly so in those prematurely born. In the latter case, the addition of as much as 10,000 units of vitamin D as obtained in concentrated fish liver oils may be important even though vitamin D milk is administered. In refractory cases of rickets in older children, it may be necessary to administer as much as 60,000 units a day for several weeks. When the disease has been controlled, the quantity is gradually diminished. Only highly concentrated fish liver oil preparations will enable us to administer these large amounts of vitamin D in small bulk.

Since viosterol contains only vitamin D it is an added reason for the superiority of the fish liver oil concentrate which contains both the fat soluble vitamins A and D. In addition, it is also an economical source of these precious ingredients.

The requirements of vitamin D in nutrition have been summarized by Jeans and Stearns (*Jeans, P. C. and Stearns, G. The Vitamins. A Symposium. J. A. M. A. 1939. The Human Requirement of Vitamin D*).

"The vitamin D requirement of the full term artificially fed baby is probably between 300 and 400 units per day.

"Normal babies receiving human milk, require less vitamin D than do babies receiving cow's milk, but how much less is not known. However, vitamin D is necessary for many and useful for most breast fed babies. It would seem wise to prescribe for them the same amount as is required by artificially fed babies.

"It is tentatively considered that prematurely born babies may require twice as much vitamin D as full term babies during the early period of most rapid growth, after which time the requirements should be the same as for babies born at term.

"For children between infancy and adolescence a daily allowance of at least 750 cc. of milk together with from 300 to 400 units of vitamin D permits consistently ample retention of calcium and phosphorus. The optimal quantity of vitamin D cannot be stated accurately, though it appears probable that the total quantity needed is neither greater nor less than the amount required for the infant.

"For adolescents a need for vitamin D exists, but insufficient data are available to permit an estimate of the quantity required. It seemed probable that from 300 to 400 units a day would be satisfactory.

"For adults the optimal amount of vitamin D, if a need exists, remains to be determined.

"It appears strongly advisable to give vitamin D during pregnancy and lactation. The optimal amount is not known. During lactation the requirement may be greater than at any other period of life and a daily dosage of 800 units or more is suggested together with an abundant intake of calcium and phosphorus."

The tremendous significance of vitamin D for nutrition is quite obvious. Unfortunately the sources of vitamin D are limited. Muscle meat, fruits, vegetables and cereals are essentially devoid of vitamin D. Even those foods such as milk and eggs which contain vitamin D, have only a comparatively small amount. Moreover,

the vitamin D content of these foods is subject to considerable variation depending on the season of the year.

Vitamin D may be best obtained from fish liver oils and from irradiation of the skin by sunlight. This latter source may also be seriously affected by the time of the year and the occupation of the individual.

Fish liver oils are therefore the most reliable source of natural vitamin D throughout every season of the year and in concentrated form may supply very large quantities of this essential food factor. Coupled with this is the fact that the fish liver oils are an excellent source of vitamin A. Halibut liver oil in particular is also among the best sources of vitamin D.

END

Changes in the Systems Affected by Allergenic Foods

By

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IN previous articles under my name, (1) it has been shown that foods are a factor in arthritis, and that there are definite changes in cutaneous reactions when a patient is allergic. The elapsed time between tests of these arthritic cases, as reported, varied from one year and one month to eight years and eight months, and the time of relief between symptoms varied from one year to eight years and four months, the average relief from symptoms being two years and four months.

In the present article the object is to show that not only do changes in sensitization take place in arthritis cases, but that a change may be exhibited in sensitivity of the respiratory system in the same individual, this being different from the former systemic disturbance.

As an illustration of these remarks, I cite the case of a patient with asthma from which he had been completely relieved, but after the lapse of time during which there were no respiratory disturbances whatever, he developed arthritis. By again making cutaneous tests and eliminating from the diet substances which gave the patient cutaneous reactions, the arthritis was completely relieved.

In this instance, due to allergenic foods, the respiratory system was first affected by asthma. Later on, in the case of arthritis, we noted disturbances in the articular and the peri-articular system.

Case 1.

Male age 40, in good health until age 38. Two years previous to consultation, the patient worked from early morning to late at night, occasionally all night and holidays. This patient on consultation was tired, weak, exhausted, depressed, with a miserable feeling in head which was hard for him to describe. He could not think clearly, had a tired, depressed sensation all along, and in getting out of bed would have to grasp some object for support. Every move was an exertion, and he wanted to remain constantly in bed, though staying in bed did not seem to rest him. His condi-

tion was growing worse, owing to the strain of the long and late hours of work, the loss of time from rest and sleep, the added accumulation of fatigue poisons, thus producing inability, disability and perversion of function. All this finally tended to divert the system from its normal functions and state of well being, to one of incapacity. Eventually the patient became a very sick man.

Cutaneous tests were made for irritant foods and diet was arranged accordingly. After one week on a diet, the patient showed some improvement, the miserable feeling became less, and in two weeks a decided improvement had taken place. In four weeks he was relieved of all disagreeable symptoms.

Four months later, this subject had luncheon with a friend, eating foods that had been proscribed as producing cutaneous reactions. On retiring he felt fagged out, was restless, and had bad dreams. In the morning, with return of all previous symptoms in head and all over the body, he stayed in bed all day. There was an improvement at night, and the following morning patient was free from depressed feelings but was still weak and exhausted. Indeed, it was ten days before this patient returned to the condition of health he enjoyed previous to the eating of this luncheon.

What could offer a more clear-cut demonstration of the cause of this man's condition than his experience with the avoidance of the foods to which he was sensitive, when there was complete relief of all symptoms, but with only one meal of forbidden foods, the reaction confined him to bed for two days and required ten days for complete recovery.

In this instance, reactions were obtained to Wheat, Chicken, Salmon, String Beans, Coffee, Banana.

The same patient appeared for another consultation May 18, 1936, for arthritis of both shoulders, right hip, right knee, which started March 1, 1936. The pains in the affected joints were acute, the slightest pressure or movement of any of these joints causing severe pain; even while sitting still there were sharp-shooting pains starting in the right hip and running down the entire leg. Patient would have tears running down his cheeks, during these acute attacks.

Cutaneous tests showed reactions to Oatmeal, Beef, Salmon, Spinach, Grapefruit, Cantaloupe, and a diet was arranged accordingly. In ten days the patient showed an improvement of 30 percent, 20 days 50 percent relief from pain in all joints, in four weeks 75 percent and in six weeks there was complete relief from all arthritic disturbances.

In this case, there was first exhibited the allergic manifestations as shown by a weak, exhausted, depressed condition in

which the nervous and muscular systems were below par. At the second consultation on May 18, 1936, the articular and peri-articular systems were involved with all the symptoms of arthritis. Thus we note a distinct change in the condition of the body, at different consultations. In each anatomic system affected, the disturbances by allergic foods were different with one exception, namely Salmon, which gave cutaneous reactions at both tests.

Case 2.

Female, age 19. Consulted me on October 19, 1925 for asthma. Asthma started at five years of age. At first the attacks lasted from three to seven days, gradually increasing in duration and severity of attacks until the last six months when she had asthma all the time. Attacks were so severe the patient was confined to bed. (History of some cardiac disturbance during the attacks.) In May, 1925, attacks were so severe that she lost sixteen pounds.

Cough preceded the onset of asthma. Patient did not raise any sputum with attacks. Eczema started at one year of age and lasted for one year, affecting the face and scalp. At three years of age had dysentery lasting three weeks. Poison ivy affected the face, arms, legs, previous to ten years of age. Had persistent sneezing, watery nasal discharge and stuffed nose, worse from April to October. Indigestion with gas and distress preceded, and asthma came on at any time, even in middle of night. Urticaria started in infancy and continued throughout life. Nasal examination showed a pale boggy mucosa with watery secretion in both nares. Rales throughout the entire lungs, urticaria and eczema on different parts of the body. Blood pressure systolic 95, diastolic 65.

Cutaneous tests were made and reactions obtained to Oatmeal, Beef, Egg yolk, Codfish, Peas, Tomato, Orange, and birch, maple, ragweed, goldenrod pollen. Diet was prescribed to patient October 21, 1925. The following day the patient complained of being chilly and the next day she coughed and wheezed with some difficulty in breathing. Expecting the usual severe attacks of asthma the mother put the girl to bed and called the family physician, who on seeing the patient remarked to the mother, "... I do not know what Dr. Turnbull did, but this girl is different from her previous attacks of asthma." The physician offered patient some medicine, and patient continued with a slight wheezing, and just a little uncomfortable breathing. After one week the physician told the mother to call the author and to mention that he was giving a bromide. The mother was advised by the author to omit the bromide and to telephone the latter's office in forty-eight hours. The girl was reported decidedly better, with no difficulty in breathing. In five days she was completely well. This patient had a chill twenty-four hours after starting the diet, this chill coming on before there was time for elimination of the allergenic substances in the system. After elimination and no intake of food to which she was sensitive the attack was very light, indeed, the lightest and shortest attack that she had had for years. With the improved condition, the blood pressure increased to systolic 118, diastolic 80, in two weeks.

The Vaso-Motor Rhinitis was perennial but was markedly increased from April to October, especially during the summer months, due to the pollen of birch, maple, timothy, ragweed, goldenrod, to which she gave cutaneous reactions. Treatment for immunization against these pollens gave complete relief. With the clearing up of the asthma, the patient was relieved of all Vaso-Motor Rhinitis, Urticaria, and Eczema. She continued free from asthma, from respiratory and cutaneous disturbances, as long as she followed the diet. But if she should eat any foods to which she was sensitive, within 24 hours she would have cough, asthma, urticaria and eczema.

The author was again consulted by this patient on September 12, 1927, for a depressed condition of body and nerves which started in June, 1927. By August, 1927, she was completely exhausted and wanted to stay in bed. The slightest exertion required great effort, causing weakness, exhaustion and marked depression. Physical examination showed weak and exhausted

patient. Laboratory findings: haemoglobin, 85; red blood cells, 4,320,000; white blood cells, 6700; polymorphonuclears 50; lymphocytes 31; transitional 3; mononuclears 7; eosinophiles 8; mast cell 1; red blood cells normal in size, shape, color; platelets normal. Fasting blood sugar per 100 cc blood, 78 mgm; tolerance blood sugar 1½ hours after 100 grams anhydrous Dextrose C P, 84 mgm per 100 cc blood. Blood calcium 11.3 per 100 cc blood. Wasserman doubtful; another Wasserman taken on October 1, 1927, negative.

Fasting urinalysis, clear, pale, Sp Gr 1010; Albumen none; sediment, a few squamous cells, an occasional round cell and a rare leucocyte. Tolerance urine, 1½ hours after 100 grams anhydrous dextrose, same as fasting urine. Basal metabolic rate, minus 8, systolic blood pressure 112, diastolic 70.

The doubtful Wasserman reaction on September 12 was probably due to the allergic disturbances in the system, as the Wasserman on October 1 was negative after the elimination of the effects of the allergic disturbances. I have seen other allergic patients in which Wasserman reaction was positive, then after elimination of the allergenic foods, become negative.

Cutaneous tests showed reactions to egg, cheese, lobster, carrot, tomato, tea, grapefruit. A diet was arranged accordingly and on the next visit September 29, 1927, she showed a decided improvement. By October 10, 1927 the patient was free from all depressing symptoms and felt like doing things. Systolic blood pressure 120, diastolic 75.

In this patient there is a history of disturbances of the cutaneous system, with urticaria as infant, eczema one year of age, and continuing through life until put on a diet by author. . . . Poison ivy sensitization previous to 10 years of age. Disturbances of respiratory system were seen in vaso-motor rhinitis and asthma starting at five years of age and continuing up to time patient was put on diet by the author. The patient continued free from disturbances of the respiratory and cutaneous system until consultation on September 12, 1927, twenty-three months following the first visit for her depressed condition. Here we note atony of the nervous and muscular system, and here again with diet arranged according to the cutaneous test the patient was completely relieved. Egg yolk gave reaction at first consultation while at second consultation the whole egg was had for patient.

The diet on the second consultation differed markedly from that of the first diet as arranged on October 19, 1925, but was accepted with confidence.

Case 3.

Female, age 52, mother of Case 2, consulted me January 26, 1926, for tired, exhausted condition. Had headaches since ten years of age which had steadily increased in severity and frequency. Asthma from two years of age to thirty-one years of age. Uremia at eighteen years of age. Headaches continuous and so severe as to confine the patient to bed three to four days out of every week. The severe attacks of headache were accompanied by acute epigastric pain which required morphine hypodermically, and she felt all used up for three to four days after these severe attacks. Did not feel well more than three days out of every month. Had a general miserable feeling and a confused mental condition, which seemed to have rapidly increased in the last six months. Much sneezing, frequently fifty times at one session. Systolic blood pressure 130, diastolic 80.

Patient was put on a diet arranged by the cutaneous test. Reactions were obtained to the following: corn, chicken, milk, codfish, peas, Hubbard squash, coffee, apple, grapes. By eliminating the allergenic foods there was 50 per cent relief of all symptoms in two weeks. In four weeks there was 80% relief, and apparent cure in six weeks.

Consulted again by this patient December 3, 1936 for arthritis, which started October 26, 1932 rather suddenly, with pain in the cervical, lumbar and sacro-iliac articulations. Pain extended from hips to the middle and inner side of both thighs for ten days previous to consultation, at which time patient was confined to bed with severe pains, being unable

to turn in bed. Six months previous to onset of arthritis had severe heartburn for two hours after each meal, this being more severe since onset of arthritis. Blurred vision for last five months. Haemoglobin 80; red blood cell count 4,840,000; white blood cell count 8850; polymorphonuclears 48; lymphocytes 35; mononuclears 10; eosinophiles 7. Red blood cells show slight achromia. Fasting blood sugar, 95 mgm per 100 cc blood; tolerance blood sugar $1\frac{1}{2}$ hours after 100 grams anhydrous dextrose C P, 151 mgm per 100 cc blood. Blood uric acid 2.95 mgm per 100 cc blood. Fasting urinalysis, clear, normal color, alkaline, Sp. Gr. 1011. Albumen none, sugar none, sediment, 13 leucocytes in every field; occasional squamous cell and bacteria. Tolerance urinalysis normal, clear, alkaline, 1013; albumen none, sugar none, sediment, sixteen leucocytes in every field; an occasional squamous cell and moderate amount mucus. Basal metabolic rate minus 12. Systolic blood pressure 141, diastolic 80.

There was marked tenderness, pain, crepitation in the shoulders, hips, knees and sacro-iliac articulations. Cutaneous tests were made and reactions obtained to rice, rye, lamb, haddock, white potato, celery, strawberry, peach, and peas. Diet arranged, avoiding foods to which sensitive and in two weeks relief from pain and tenderness in the affected joints. In four weeks there was relief from arthritis and other symptoms. The important point to be brought out in this case is that at the first consultation, the symptoms of prostration with headaches and sneezing, which showed a disturbance of the nervous muscular and upper respiratory system, cleared up completely. At second consultation, seven years later, her symptoms were arthritis, blurred vision, heartburn, showing disturbances in the articular, gastric and visual systems. I have frequently seen marked improvement in vision of patients with allergic conditions.

All symptoms cleared up completely by avoiding foods to which she was sensitive and diets were different at each test.

Case 4.

Male, father of Case 2, and husband of Case 3, age 57 years. Consulted the author February 18, 1929 for arthritis, eczema, headaches, and cough; eczema of the scalp and neck all his life. Arthritis began July 1927, affecting the cervical vertebrae. Six abscessed teeth extracted and tonsillectomy fourteen months previous to this consultation, but no relief from arthritis, eczema, headaches, cough. Headaches for many years at intervals when he frequently sees red streaks. Has a persistent cough, more in the mornings. Had a nervous breakdown in 1913, absent from work for six months. Sleeps well, not tired in the morning, works at high pressure during the day. Had eczema, the whole scalp being markedly inflamed, scales, redness over vertex, redness back and sides of neck, pain, tenderness, crepitation in cervical vertebrae, both shoulders, very severe in left shoulder, great pain and marked crepitation in all joints.

Haemoglobin 80, red blood cell count 4,580,000, white blood cell count 6900; polymorphonuclears 59; lymphocytes 33; transitional 4; mononuclears 2; basophiles 1; eosinophiles 1. Fasting blood sugar per 100 cc blood 88 mgm; tolerance blood sugar per 100 cc blood, $1\frac{1}{2}$ hours after 100 grams anhydrous dextrose C.P.; 103 mgm per 100 cc blood. Blood uric acid per 100 cc blood 3.80 mgm. Wasserman negative. Urinalysis: Fasting, clear, straw color, acid, Sp Gr 1018. Albumen slight trace, sugar none, sediment, slight trace pus, one finely granular cast, occasional round cell, and squamous epithelium. Tolerance urinalysis, pale, clear, acid, sp gr 1018; albumen, slight trace; sugar none; sediment same as fasting urine. Basal metabolic rate, minus 7, systolic blood pressure 140, diastolic 80.

Cutaneous test exhibited reactions to wheat, American cheese, halibut, kidney beans, asparagus, olives, chocolate, plums. Avoiding foods to which sensitive, at next visit March 7, 1929, there was less itching of scalp and neck, less pain and crepitation in the joints. These conditions continued to improve and by April 6, 1929, the arthritis and eczema had completely cleared up.

Consulted second time June 19, 1934. This patient while going home from his work with his son was suddenly seized with severe pain in chest, gasped for breath and fell unconscious on the floor of automobile. This was diagnosed as coronary occlusion. He was seriously ill and was attended by cardiologist. The patient recovered from this after long illness. At time of this second consultation the patient was very cross, irritable, depressed, difficult to live with and took no interest in anything whatever, just sitting around the house or yard. Previous to the coronary occlusion the patient had been a very peaceful man, easy to get along with and never complained of anything, of even disposition, bright and cheerful. A complete change had taken place in this man's general appearance and actions.

Haemoglobin 95; red blood cells 5,110,000; white blood cells 8200; polymorphonuclears 59; lymphocytes 33; eosinophiles 8; fasting blood sugar per 100 cc blood, mgm 90; tolerance blood sugar per 100 cc blood $1\frac{1}{2}$ hours after 100 grams anhydrous dextrose C P, 125 per 100 cc blood. Blood uric acid per 100 cc blood 4.7 mgm. Fasting urinalysis pale, cloudy, acid 1016; albumen slight trace, sugar none, sediment, occasional pus cell, small clump of pus. Basal metabolic rate plus 7. Blood pressure systolic 120, diastolic 75. Cutaneous tests were made and reactions obtained to oatmeal, pork, chicken, mackerel, beets, broccoli, peas. Patient avoided food which gave reactions, and in one week he felt and acted, and looked entirely different. The irritability and depression were decidedly reduced so much so that all his friends remarked on the very definite change for the better. In two weeks he was the cheerful man that he had been previous to the onset of the coronary occlusion. In October 1934, a letter to the author stated that he was well, working every day, and the cardiogram taken one week previously showed a distinct improvement over the one taken six months previously.

This patient first consulted me for arthritis, eczema, headaches, cough, none of these symptoms being relieved by extraction of six abscessed teeth and tonsillectomy fourteen months previous to this consultation. All these conditions cleared up as by magic, through avoidance of foods to which he was sensitive.

At time of this first consultation, there was involvement of the cutaneous, cerebral and respiratory systems as evidenced by cough, and also of the articular system. At the second consultation October 1934, we have involvement of the nervous and cardiovascular systems. The nervous system manifested its changes in function in irritability and a sense of mental depression, general lack of interest. Here also the improvement is subsequent to a complete change from foods to which patient is sensitive.

Regarding the coronary thrombosis in "Allergy As A Factor In Thrombosis" I have stated that cases of phlebitis, blocking of femoral artery and vein, were completely relieved of the pain, tenderness, with absorption of the coagulation. Angina pectoris was completely relieved, as also the cardiovascular disturbances, but if these patients should eat any of the foods to which they were sensitive, in from four to forty-eight hours after eating they would have a return of their cardiovascular symptoms, such as pain, soreness, tenderness, blocking of femoral artery and vein, and angina pectoris. In the case of angina pectoris, the attack started four hours after eating salmon, the symptoms reached their apex in twenty-four hours, then gradually receded so that after five days of strict adherence to diet patient was free from pain and all evidence of cardiovascular disturbances.

Case 5.

Female, age 39. Consultation March 21, 1918 for frequent colds, sneezing, watery nasal discharge for eighteen months, worse during June, July, August, September. Had a bad cold March 1917 and cough from December 1916 to August 1917. This patient was tested for pollens, animal pets. With this history of sneezing, watery nasal discharge which was worse during June, July, August, September, one would expect to find the pollens the cause of the disturbances during these

summer months, but no reaction was obtained in testing with pollens which prevail during this time. Cutaneous reactions were obtained to beef, salmon, lobster, shad, spinach, banana and by avoidance therefrom complete relief of all symptoms followed. As the allergenic fish were eaten during the summer months, these were the cause of the sneezing, watery nasal discharge during June, July, August, September, which proved the correctness of the negative skin test to pollens and showed how one can be deceived in such a case by the history of vasomotor rhinitis. A patient may have hay fever but no pollen reactions, and complain that the nasal passages are sensitive, but not the cutaneous system. This patient was sensitive to beef and wished to be desensitized to it, which was done very satisfactorily.

Same patient consulted me March 26, 1922. Her symptoms at this time were lassitude and mental confusion, abdominal distention, noises in ears, as roaring; sizzling, as of steam letting off; pains all over the body, from head to toes. The patient was perfectly well as long as she followed the diet as arranged by test of 1918. As she had no return of the upper respiratory symptoms in the latter part of 1919, she began to eat miscellaneous foods, disregarding the diet which had completely relieved all the symptoms at time of consultation 1918. Soon other symptoms occurred. On account of the abdominal distress, distention, gastrointestinal symptoms, she was advised to have her gall bladder and appendix removed, which operation was performed March 1920. After these operations the patient's condition grew rapidly worse with increasing weakness, depression, and confusion. Talking with patient caused much mental confusion, so that the patient was unable to answer questions. Since January 19, 1922 she has a tendency to fall either to the right or left. This condition came on suddenly, and on standing with feet together, eyes closed, the patient would sway in a wide angle. It was necessary for someone to be near to keep her from falling. With eyes closed she was unable to touch the tip of her nose with her fingers. Vertigo was very marked and occurred several times a day. . . In getting into bed had a feeling as though falling, but this disappeared after being in bed a while. The vertigo would start upon getting out of bed or from rising from a sitting position. September 1921, was nauseated for seven weeks, vomiting mucus and bile every morning. August 19, 1921, patient had eaten oysters which was followed in eight hours by marked swelling of the face, eyelids, and aching all over body. This patient had consulted numerous excellent physicians and a neurologist without any relief.

There were increases of all reflexes. On cutaneous tests, reactions were observed to: white flour, corn, beef, turkey, cheese, haddock, herring, sardines, salmon, oyster, peas, beets, carrots, spinach, celery, peppers, tea, orange, raspberry, banana. Patient avoided these allergenic foods and in ten days the abdominal distress and distention were relieved and then began a gradual clearing up of all the other symptoms, the vertigo, noises in ears, abdominal distress and distention, nausea, vomiting. She became free of pains and lassitude and mental depression suddenly vanished. Now she could stand with feet together, eyes closed without swaying, and with eyes closed could readily touch tip of her nose. But should this patient consume any of the specific foods to which she was sensitive, the symptoms would indubitably recur.

In this case, at the first consultation we found disturbance of the respiratory tract as shown by sneezing, watery nasal discharge, cough, which symptoms were all relieved by avoiding the banned foods. At the second consultation March 1922, the patient exhibited disturbance of the cerebral, nervous, gastro-intestinal, aural, systems thus showing a syndrome of different systems affected from that of first consultation four years previously. Here we note a change in systems affected and also change in susceptibility to certain foods. Beef, to which she was allergic at the first consultation, in March 1918, to which food she was desensitized at that time, gives a reaction at second consultation four years later, showing that after a lapse of time she had lost the effects of the previous desensitization. I have therefore discontinued desensitizing patients to certain foods, realizing that with time changes occur

in some way within the system and the patient may again become sensitive to these very same foods.

Case 6.

Male, age 29, single. Consulted me May 14, 1926. Always sick as a child, poor health all his life, had never been robust, lost 26 pounds in last six months. Always weak, tired readily, mentally confused, depressed. For one year suicidal and homicidal tendencies, trying at times to take his own life and that of his attendant. Dizziness at intervals for one year, and a feeling of falling forward when walking, with a swaying to either right or left. Felt too tired out to get up in the morning, but after being up a while felt a little better, but at one point was again prostrated and had to lie down; after five p.m. utterly unable to move around.

Haemoglobin 85; red blood cells 5,320,000; white blood cells 6600; polymorphonuclears 65; lymphocytes 23; mononuclears 2, transitional 5, basophiles 1, eosinophiles 4, red blood cells showed slight variation in size. Fasting blood sugar per 100 cc blood 94 mgm. tolerance blood sugar 1½ hours after 100 grams anhydrous dextrose C P 161 mgm Wasserman negative. Fasting urinalysis, normal color, clear, acid, Sp Gr 1014, albumen none, sugar none, sediment, one finely granular cast, a rare leucocyte, round and squamous mucus. Tolerance urine, 1½ hours after 100 grams anhydrous dextrose C P, pale, clear, acid, 1004, albumen none, sugar slight trace, sediment an occasional red blood cell, a rare leucocyte, round and squamous cells. Basal metabolic rate minus 25. Blood pressure, systolic 160, diastolic 70.

In these examinations there is high blood sugar in tolerance test, with some coming through in tolerance urine, low metabolism, and high systolic blood pressure, with minus 25 metabolism. One might think of thyroid medication, which in my opinion is not justified with this type of patient.

On cutaneous test being made, reactions were obtained to: wheat, beef, American cheese, mackerel, cream cheese, pea beans, lettuce, blueberry, peach. Patient following instructions, by June 12, 1928, was feeling much better, sleeping better, not tired, less mental confusion, no suicidal or homicidal impulses during the last ten days. He continued to improve so that by July 1, 1928 he was free from mental confusion, suicidal and homicidal tendencies. The patient declared at this time "I am in the best condition physically and mentally that I have ever experienced."

Patient again consulted me on September 22, 1931 for arthritis affecting cervical articulations, shoulders, hips, knees, which started six months ago. This had become rapidly worse in the last two months, causing pain, greatly increased with motion. . . . Cutaneous test found patient sensitive to: rice, lamb, salmon, beets, coffee, cocoa, grapefruit, apple, honey, melon. With the right diet in two weeks there was less pain and stiffness in the joints. . . . In four weeks there was 75 per cent improvement and in six weeks complete arthritic relief.

This patient at first consultation appeared tired out and depressed mentally, with suicidal and homicidal tendencies. In this phase, the cerebral nervous, muscular systems are involved. Three years and three months later at second consultation, none of the symptoms previously so pronounced was in evidence but this time the articular system was affected in form of arthritis, thus showing the versatile effects of a disagreeing diet on body and personality.

Case 7.

Female, age 67. Consultation on June 11, 1931 for arthritis, which started 1919, following a tonsillectomy and had been rapidly growing worse, involving the cervical articulations, both shoulders, knees, hips, and right big toe. Pain often so severe as to confine patient to bed. Phalangeal articulations of both hands markedly enlarged, with great deformity. Seasons, as cold weather, had no influence that the patient noticed. Arthritis first started in the shoulders, then the wrist, ankles, tarsal, metatarsal, carpal, metacarpal knees then phalanges of

both hands and feet, plantar and posterior surfaces of both Os Calcis. Tenderness and crepitation of all joints affected, there was marked deformity and enlargement of metacarpal and phalangeal articulations of both hands.

Cutaneous test indicated reactions to pork, egg-white, cod-fish, string beans, tomato, lettuce, orange, banana, cantaloupe, clam, grapes. After avoiding foods to which found sensitive on June 25, 1931, joints less painful, less swelling, so that the rings slipped off fingers easily. July 8, 1931, condition improved 75 per cent; July 26, 1931 complete relief of all pain, and discomfort in all joints.

Haemoglobin 80; red blood cells 4,100,000; white blood cells 8700; polymorphonuclears 60; lymphocytes 22; mononuclears 7; transitional 2; eosinophiles 6; basophiles 3. Fasting blood sugar 90 mgm per 100 cc blood. Tolerance blood sugar 1½ hours after 100 grams anhydrous dextrose C.P., 160 mgm per 100 cc blood. Blood uric acid 7.2 mgm per 100 cc blood. Nonprotein nitrogen 36. 3 mgm per 100 cc blood. Wasserman negative.

Fasting urinalysis, straw color, cloudy, slightly acid, Sp Gr 1020; albumen slight trace; sugar, trace; sediment, many pus cells, red blood cells and squamous epithelium. Tolerance urine cloudy, straw color, strongly acid sp gr 1020. Albumen trace, sugar plus 1, 33 pus cells, red blood cells. Basal metabolic rate minus 6. Blood pressure systolic 178, diastolic 90.

Some time after being completely relieved of all disturbances, the patient ate steamed clams at night, and the following morning was awakened with severe pain and swelling in the right big toe which cleared up in 48 hours. At the time of test, clams gave a reaction and the patient was instructed to avoid them but feeling so well she thought that they were safe. This sharp reaction was conclusive proof to the patient of the accuracy of the cutaneous test. A letter was received October 1935 stating how well patient was, free from all arthritic disturbances, walking from three to five miles with comfort.

Was consulted by this patient on September 14, 1937 for sore throat and a feeling of stiffness in the throat with thickness of voice, bad taste in mouth, a sensation of swelling in throat, with difficulty in swallowing, and also dizziness. These symptoms started in January 1937; had consulted nose and throat specialist and received treatments without any relief.

Haemoglobin 100; red blood cells 4,240,000; white blood cells 8000. Polymorphonuclears 55; lymphocytes 41; mononuclears 4. Fasting blood sugar 93 mgm per 100 cc blood; tolerance blood sugar 1½ hours after 100 grams anhydrous dextrose C.P.: 230 mgm per 100 cc blood. Blood uric acid per 100 cc blood 5.32 mgm. Fasting urine light straw color, 1012; albumen none, sugar none, acid, sediment 5-10 white blood cells in field, mucus, crystals, urates, bacteria. Tolerance urine same as fasting except few red blood cells.

Basal metabolic rate minus 6; Wasserman negative, blood pressure systolic 140, diastolic 80.

Cutaneous test reactions obtained to oatmeal, beef, haddock, white potato, escarol, grapefruit, apple, rhubarb, casaba melon. With diet arranged accordingly in two weeks there was fifty-per cent relief from sore throat, swelling, thickness of voice. In four weeks there was complete relief of all throat symptoms, and patient could readily swallow foods.

Here on first consultation she had a disturbance of the articular system which was completely relieved by diet, and at the second consultation, two years and three months later there were disturbances of the mouth pharyngeal, and laryngeal mucosa, shown by bad taste in mouth, sore throat, stiffness in the throat, difficulty in swallowing, and a thickness of voice. These symptoms were all relieved by diet. On this second consultation we observe another system affected, an entirely different syndrome.

Case 8.

Female age 25. Consulted me September 15, 1926, for epileptic attacks which started at seven years of age, then lapse of five years before another attack. These attacks had

continued since the second attack every night, lasting 10-15 minutes. Had attacks frequently during the day; the tongue usually bitten during attacks and bleeds freely. Goes to sleep immediately after attacks, does not remember anything about attacks, and feels exhausted for twenty-four hours after attacks. Patient thinks there may have been some attacks in interval between first and second attack, as these occur at night, and frequently blood would be found on the pillow. Urticaria at 11 and 12 years of age, has itching of the abdomen, pimples on back. Menstruation began at 12 years of age, 28 day interval, last 4 days, slight pain at beginning of each period during the last year. No evidence of attacks being greater during or just before menstrual period. Mother has headaches.

Haemoglobin 83%; red blood cells 5,152,000. White blood cells 8,400. Polymorphonuclears 65; lymphocytes 23; mononuclears 2; transitional 7; eosinophiles 3. Fasting blood sugar 117 mgm per 100 cc blood. Tolerance blood sugar 149 mgm. Fasting urine, pale, clear, neutral, Sp Gr 1008. Albumen none, sugar none. Sediment, occasional squamous cell, and rare round cell. Tolerance urine, pale, clear, acid, Sp Gr 1008. Albumen none, sugar none. A few squamous cells, occasional round cell, one round cell, rare leucocyte. Plus 12. Blood pressure, systolic 120, diastolic 60.

On cutaneous test, reactions showed to: corn, chicken, oyster, celery, peas, coffee, oranges, apple. Diet arranged. Had one attack on October 2, 1926, at night, after having had lunch away from home. Two days later eating forbidden food, had itching of abdomen. After this was completely free of any epileptic attack or itching of abdomen, until six months later ate small piece of apple pie with her lunch, and that night had severe epileptic attack with itching of the abdomen. Had no epileptic attack since this.

Again consulted February 26, 1930, patient had itching of both ears, back of ears; and in the throat this condition was present for four weeks, and rapidly getting worse.

Haemoglobin 85%; red blood cells 4,710,000; white blood cells 8000; polymorphonuclears 65; lymphocytes 26; mononuclears 4; transitional 4; eosinophiles 1. Red blood cells show few crenated, otherwise normal. Fasting blood sugar 105 mgm per 100 cc blood, tolerance blood sugar 128 mgm per 100 cc blood. Blood uric acid 2.58 mgm. Urine, straw color, acid, sp gr 1012; albumen trace, sugar none. Sediment, few pus cells, few free leucocytes, one round cell. Basal metabolic rate minus 2. Blood pressure systolic 120, diastolic 70.

Cutaneous reactions obtained to following: lamb, halibut, lobsters, sweet potato, tomato, tea, blackberry, plum, almond, nut and a selective diet arranged. The itching in throat, back of ears, and in ears was 75 per cent relieved in two weeks and in three weeks completely relieved. August 24, 1930 patient ate lobster, and this followed in eight hours by severe itching of the auditory canal, ears, back of ears and throat.

In this case there is epilepsy which has been present for eighteen years. The cerebral system is in this instance affected, with disturbances in muscular system. These attacks were completely relieved by diet, except for the eating of small piece of apple pie, to which the patient was sensitive which brought on an epileptic attack and itching in the abdomen. At the second consultation there is found a persistent itching of ears, auditory canal, back of ears, also the mucous membrane of back of throat. There were no epileptic attacks, although at both consultations there was itching of cutaneous system which affected different parts at different times. At second consultation the throat was involved in addition to cutaneous system.

Case 9.

Female, age 36. August 6, 1931. Had headache all her life, which begins with blurr, and zig-zag visual disturbances, followed by nausea, pain beginning in the eye-balls and radiating to temples, then vortex, sometimes starting in the occipital region. These severe attacks of pain come twice a month with no particular relation to menstrual periods. Headaches last 5-6 days; never completely free of headaches. Menses

began at 16 years of age; during the first six months very irregular, then 28 day interval. Pain begins twenty-four hours previous to flow; severe pain for two days at start of flow; pain so severe as to incapacitate the patient, confined to bed. These periods last from 3-5 days; flow has been scanty until this last year. Had urticaria in April 1930, tired every morning and tired easily for last ten years. Mother has headaches and arthritis.

Haemoglobin 75%; red blood cell count 4,420,000, white blood count 7900, polymorphonuclears 75; lymphocytes 12; mononuclears 5, transitional 4, eosinophiles 4. Red blood cells show considerable achromia, and slight polychromatophilia platelets normal. Fasting blood sugar 112 mgm per 100 cc blood, tolerance blood sugar 141 mgm per 100 cc blood, blood uric acid 3.52 mgm per 100 cc blood.

Fasting urine, small amount, straw color, slightly cloudy, sp gr 1022, alkaline. Albumen none, sugar none, phosphates, leucocytes, round cell, squamous. Tolerance urine, straw color, clear, alkaline, sp gr 1022, albumen trace, sugar present. Sediment, rare red blood cell, one leucocyte, round cell, many pus cells.

Cutaneous reactions were obtained to: egg, milk, halibut, yellow eye bean, mushrooms, raspberry, banana, peanuts. With diet arranged according to test, on September 6, 1931 patient feels well; had two slight headaches. Since starting with the diet, 50% less pain with menstruation, does not tire easily. October 17, 1931 reports no headache, no pain or disturbances with menstrual periods. If she should eat any foods to which sensitive, will suffer headache, nausea, vomiting.

Was consulted by this patient again October 1933 for eczema of face and acne about the shoulders and back, which symptoms have been present for three months.

Haemoglobin 75%; red blood cell count 4,290,000; white blood cells 7100; differential cells. Polymorphonuclears 43; lymphocytes 46; endothelium 7; eosinophiles 4. Fasting blood sugar, 96 mgm tolerance blood sugar, 150 mgm. Blood uric acid 3.60 mgm.

Fasting urine, clear, normal, color, slightly alkaline, sugar none. Albumen none. Sp Gr 1013; sediment, rare leucocyte, occasional squamous cell. Tolerance urine, clear, pale straw, sp gr 1005, slightly alkaline, albumen none. Sugar present 1+ few leucocytes, rare squamous cell. Basal metabolic rate minus 1. Blood pressure, systolic 110, diastolic 60.

Cutaneous tests were made and reactions obtained to: oatmeal, milk, oyster, white potato, onion, broccoli, olives, blueberries, apricots. On an arranged diet, in two weeks there was 50% improvement in the eczema of face and acne about shoulders and back. In four weeks the eczema and acne had completely cleared up.

In this instance, we note at first consultation cerebral disturbances in the form of headaches, in the ocular system with a blurred and zig-zag vision and pain in the eyeball. Nausea marks a disturbance of the gastrointestinal tract. Disturbance of the genital tract by painful menstruation. These conditions were completely cleared up by diet, and patient remained free of disturbances until ingesting allergenic food. On the second consultation, we note a cutaneous eruption, shown by eczema of face and acne of shoulders and back, which was rendered completely clear by following the diet.

Case 10.

Male, age 10 years. Consultation on September 12, 1930. Asthma started at 3 years of age, attacks lasted three days, at intervals of two months between attacks. Very severe attacks started and have continued since September 1926. Had a hard dry cough, attacks were continuous, frequent coughing spells every day but did not raise any sputum. Sneezing preceded the onset of the first attack of asthma and has continued since then. Asthma worse preceding and during storms and high humidity. Epigastric pain with asthma. Headaches preceded the asthma by 24 hours and continued throughout the severe attacks. No history of asthma in family. Paternal grandmother had arthritis.

Haemoglobin 75%; red blood cell count 5,332,000; white blood cells 7900; polymorphonuclears 51; lymphocytes 25; mononuclears 3; transitional 8; mast 2; eosinophiles 11; fasting blood sugar 88 mgm per 100 cc blood; tolerance blood sugar 128 mgm per 100 cc blood.

Fasting urine, small amount, normal color clear, acid, sp gr 1018, albumen trace, sugar none. Sediment; considerable mucus, one fine granular cell, a rare red blood cell and leucocyte, occasional round cell and squamous.

Basal metabolic rate minus 10. Blood pressure, systolic 100; diastolic 65.

Reactions by cutaneous test were obtained to lamb, milk, scallops, white potato, string beans, spinach, pepper, orange, chocolate, filbert nut, reactions to pollen of timothy, ragweed, goldenrod and also tobacco. Selective diet was arranged accordingly. Patient was desensitized to timothy and ragweed pollen. In two weeks after being on diet, patient was 60% free of asthma, in three weeks completely so. Desensitization to pollen with excellent results, as the patient had no trouble during the pollen seasons.

Again consulted by patient September 12, 1933 for eczema, which started six months previous to consultation. The eczema involving whole face, scalp, both arms, back with crust formation on the face, arms. All the affected parts were greatly swollen. There was marked redness of the mucous membrane of both nares, post pharyngeal and laryngeal mucosa.

Haemoglobin 90%; red blood cells 5,190,000; white blood cells 9100; polymorphonuclears 65; lymphocytes 25; mononuclears 3; basophiles 2; endothelium 3; eosinophiles 2. Fasting blood sugar per 100 cc blood 80 mgm. Tolerance blood sugar in 100 cc blood 100 mgm.

Fasting urine light yellow, clear, acid sp gr 1020, albumen none, sugar none, sediment, leucocytes, squamous cells. Tolerance urine light yellow, clear, acid, sp gr 1024, albumen none, sugar none, sediment considerable mucus, squamous cells. Blood pressure systolic 100, diastolic 70.

Cutaneous test reactions were obtained to: corn, rye, cheese, egg, herring, clam, tomato, white potato, honey, grapefruit, apple, fig. Thanks to a selective diet, in two weeks there was 60% improvement in the eczema and in four weeks the skin was normal. Here at first consultation this patient had disturbances in the entire respiratory tract, as shown by sneezing, cough, asthma; while at second consultation there was severe and marked eczema. Both the respiratory and cutaneous system derangements were completely cleared up by diet.

RESUME AND COMMENTS

Case 1.

Male, age 40. First consultation, tired, depressed, could not think clearly, felt mean all over, wanted to stay in bed, but staying in bed did not rest him, getting out of bed had to grasp some object for support; long hours of work, added strain and accumulation of fatigue poison diverted system from normal function, causing cerebral, nervous, muscular disturbances.

Second consultation 3 years after first consultation developed arthritis.

Case 2.

Female, age 19. Had eczema 1 year of age, lasted one year; dysentery three weeks; poison ivy, affected until 10 years of age; perennial sneezing, worse during June, July, August, September; attacks urticaria since infancy; asthma since five years of age. In this patient there is a history of allergy from one year of age up to time of consultation.

Second consultation 23 months later; symptoms: tired, weak, exhausted, depressed. At both consultations,

there was high blood sugar tolerance, being 84-mgm; low polymorphonuclear, high lymphocyte and eosinophilia count, low blood pressure, which became normal. This patient had doubtful Wasserman, but after being on a diet became negative.

Case 3.

First consultation, mother of case 2, symptoms: Weak, depressed, headaches, confused mentally, sneezing, blood pressure, sys. 150, diast. 80. Second consultation 10 years later; arthritis, heartburn, blurred vision, low polymorphonuclear, high mononuclear, eosinophilia.

Case 4.

Male, age 57, husband of Case 3, father of Case 2. Symptoms: arthritis, eczema, headaches, cough, with headaches sees red streaks; 14 months previous had six abscessed teeth extracted, and tonsillectomy without relief. Second consultation after five years, following coronary occlusion, was irritable, cranky, depressed, difficult to get along with.

In these three cases 2, 3, 4, daughter, mother, father; mother with history of asthma as child, later weak, exhausted with headaches. Father, arthritis, eczema, headaches. Is it any wonder that the daughter was allergic from one year of age?

Case 5.

Female, age 39. Frequent colds, sneezing, watery nasal discharge for 18 months sneezing worse during June, July, August, September. No reaction obtained for pollen, the increased sneezing during summer being due to eating fish.

Second consultation four years later. Tired, weak, depressed, abdominal distress and distention; pains all over body, mentally confused, swaying if standing with eyes closed, either to right or left; cholecystectomy and appendectomy failed to relieve condition, but symptoms became rapidly worse. Here we note disturbances of cerebral, nervous, nasal, gastrointestinal systems.

Case 6.

Male, age 29. Depressed, homicidal and suicidal tendencies, feeling of falling forward with walking, with sway to either right or left in rising from sitting position; low tolerance blood sugar; low metabolism, minus 25. Second consultation five years later, has arthritis which started six months previously.

Case 7.

Female, age 67. Arthritis started 12 years ago, following tonsillectomy; fasting blood sugar 90 mgm. with trace sugar in fasting urine, high blood uric acid, pus cells, red blood cells in urine. Tolerance blood sugar, 160 mgm. Blood pressure 178, diastolic 90. Consulted second time six years later, sore throats, continuously, bad taste in mouth, feeling of stuffiness in throat, thickness of voice, difficulty in swallowing, dizziness, high lymphocyte, low tolerance blood sugar 230 mgm. Although with this high blood sugar, no sugar in tolerance

urine. At first consultation blood pressure 178/90 while at second consultation 140/80. Blood uric acid, still high but 1.9 mgm less than at first consultation.

Case 8.

Female, age 25. Epileptic attacks started at 7 years of age, attacks frequently every day and night, itching of abdomen, high fasting blood sugar, 117 mgm tolerance 149 mgm. Low blood pressure, Sys. 100, diast. 60. Second consultation three years later, itching both ears, back of ears, auditory canal; tolerance blood sugar 128 mgm against previous tolerance 149 mgm.

Case 9.

Female, age 36. Headaches all life, begins with blurring and zig-zag visual disturbances, pain in eyeballs, radiates to temples, vortex sometimes occiput, never completely free of headaches. Dysmenorrhea severe pain 24 hours before flow, continues during the period, confined to bed during the menstrual period. Polymorphonuclears high, 75, fasting blood sugar 112, tolerance blood sugar 141, low lymphocyte count, tolerance urine sugar 1. Second consultation, 2 years 2 months after first consultation. Eczema of face, acne shoulders and back. Polymorphonuclears now low, 43, lymphocytes high, 46, fasting blood sugar 96 mgm, reduction of 16 mgm tolerance blood sugar, about same as first consultation, no sugar in tolerance urine.

Case 10.

Male, age 10. Asthma which started at 3 years of age, attacks at two months intervals lasting three days, attacks become more severe and have been continuous since four years of age; hard dry cough, frequently during the day, does not raise anything; epigastric pain with asthma, headaches precedes and continues during the severe attacks, asthma worse during high humidity days before and during storms; high eosinophiles 11, fasting urine, trace albumen. Second consultation three years after first consultation, eczema, started 6 months previously, involving face, scalp, arms, back, with crust formation.

COMMENT

In this series of cases there are many systems of the human body affected, such as the *cerebral*, as shown by an exhausted or depressed state with mental confusion, confusion of ideas, headaches, epilepsy, suicidal and homicidal tendencies; swaying in walking, feeling of falling forward in walking and with eyes closed swaying in a wide angle. *Visual* system; blurred vision, red streaks, and zig zag vision. *Olfactory* system: sneezing, watery nasal discharge, hay fever. *Aural*: noises in ears, as knocking, roaring, steam letting off, eczema of ears and auditory canal, vertigo. *Oral*: bad taste in mouth. *Post pharyngeal, pharyngeal, laryngeal*: redness musosa, thickness of voice, difficulty in swallowing. *Respiratory*: Trachea, bronchi, bronchioles cough, asthma. *Gastro-intestinal*: heart-burn, gas, distress, distention. *Genital*: Dysmenorrhea.

Articular, as arthritis. *Cutaneous*, as Eczema, urticaria, acne. *Muscular*: Weakness, pains. *Vascular* system as shown by effects on blood pressure, raising the low pressures, lowering the high pressure. *Coronary*, as shown by case 4, who had coronary occlusion; later on, after diet arranged, cardiogram showed greater improvement than had taken place in previous cardiograms. *Blood changes*, by changes in differential cell counts, blood uric acid, tolerance blood sugars.

CONCLUSIONS

1. Allergy can affect any system in human body, being almost as protean in its phenomena as syphilis.
2. There can be different systems affected at same time, depending on various reflex effects of allergy.

3. Different systems can be affected after an interval from those previously affected.
4. With the changes in system or systems affected, there will be changes in the group of allergenic foods.
5. When the allergenic foods are avoided there is relief from symptoms.
6. If any allergenic foods are eaten, there is a return of symptoms.
7. Allergenic foods can alter functions of human systems.
8. History is important, but in some cases may be misleading, and give the impression that cutaneous tests are not reliable.
9. With thorough knowledge of allergy, making the cutaneous test, reading the test, one can rely on those findings.

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8. Turnbull, John A. "A Disturbance Caused By Proteins," *Boston Medical and Surgical Journal* clxxii No. 20, May 13, 1920, 493-497.

Book Reviews

Principles and Practices of Inhalational Therapy. Alvan L. Barach, 315 pages, 59 illustrations, (\$4.00). Philadelphia, J. B. Lippincott Co, 1944.

This timely book brings into one volume a digest of the numerous advances that have been made in inhalational therapy since Barach first introduced the therapeutic use of helium in 1934.

There are thirty-eight chapters most of which consider specific disease processes and their treatment. Each chapter opens with a discussion of the pathologic physiology of the condition in question. These discussions are beautifully done and provide the rationale for the treatment.

It is nothing short of amazing that in spite of the noteworthy advances in this field there are still those who refuse to see the benefits or admit the criteria for application of inhalational therapy. Some individuals, for example, still administer nitrous oxide without oxygen, either failing to realize the presence of anoxia or refusing to admit its deleterious effects. A point to be emphasized is that even when the arterial oxygen saturation is 96 percent one can not assume that the patient does not suffer from anoxia. The driving force for the transfer of oxygen to the tissues is determined by the amount of the gas in physical solution (i.e. the tension) and not by the quantity held in chemical combination by hemoglobin. In a reported case of con-

gestive heart failure the arterial oxygen saturation was 96 percent. Nevertheless compensation was regained following four weeks of continuous oxygen therapy although previous bed rest and routine measures had accomplished little or no improvement. One cannot depend upon cyanosis as a criterion for administering oxygen. Cyanosis is due to reduced hemoglobin in the blood and appears only when the concentration of this substance reaches a certain amount. An anemic individual, therefore, may not accumulate sufficient reduced hemoglobin for cyanosis to appear and yet suffer from severe anoxia. The various criteria for administering oxygen are discussed by the author and rest on a sound scientific basis. These facts are indisputable and should not be confused with arguments revolving about the empirical aspects of the subject, such as the quantity, rate and time and special technique of administration.

The beneficial results obtained in pulmonary edema by breathing gases against positive pressure rest on some interesting physiologic facts. The hydrostatic pressures which obtain in the pulmonary circulation are actually less than the colloid osmotic pressure of the blood proteins. According to Starling's theory, therefore, there should be no interstitial fluid in the lungs and any condition which raises the hydrostatic pressure even slightly should dispose toward edema of the

lungs. Therefore, breathing against positive pressure tends to offset the effective filtration pressure. It is of interest in this connection that when obstruction to the respiratory effort is suddenly relieved edema of the lung often results.

The author is of the opinion that proprioceptive reflexes have been over-emphasized in dyspneic states. He writes "Although the heightened pulmonary ventilation after exercise had been ascribed to reflex causes, studies on normal men have proven that the effective stimulus was chemical and not reflex. When subjects walked on a treadmill, total ischemia of both legs resulted in a marked fall in pulmonary ventilation, even though the nervous pathways were intact. Release of the ischemia was followed at once by a marked hyperventilation." With regard to the first part of the statement it is well known among physiologists that the hyperpnea resulting from physical exercise (without accumulation of any chemical stimulus in the blood) is many times more intense than that obtained by the highest concentrations of carbon dioxide stimulatory to respiration (approximately 9%). The treadmill experiment is difficult to interpret but one recalls the experiments of Harrison and Coworkers (quote from Bard, *Physiology in Modern Medicine*, p. 605, 9th Ed.):—" . . . breathing was found to be stimulated when one hind leg was moved passively, even though the femur was severed, the femoral vessels clamped, and the leg connected with the body only by the sciatic nerve: when the nerve was cut, movements of the leg had no effect on breathing whether the femoral vessels were closed or open. These experiments show, not only that the factor responsible for the observed hyperpnea was not a chemical one acting on the center, but also that it was brought into action by movement of the affected limb; its absence after section of the nerve identifies it as a reflex . . ." Dyspnea (a subjective sensation of increased breathing) cannot always be distinguished from hyperpnea. The experiment cited by the author, therefore, does not support his thesis as well as the observation that cardiac dyspnea is decreased by inhaling oxygen even when an increase in congestion of the lung occurs (assuming that the author has differentiated between hyperpnea and dyspnea in his own thinking).

The author appears to interpret the work of Dean and Visscher as an attack on his conclusions (p. 90). It would appear to the unbiased observer, however, that Dean and Visscher have made a more critical study. They conclude, on the basis of an elaborate physical study, that less work is required to move a helium mixture because of its lower turbulent velocity and higher critical velocity. The presence of turbulence means an increase in viscous work. The word "viscance" is used by Dean and Visscher to denote the viscosity effects of a system comprising the conducting tubes as well as the gas mixture in question. The word viscosity refers to a quality of the gas only and is expressed in the absolute unit known as a poise. The explanation of Barach rests on the differences in specific gravity of the oxygen-nitrogen mixture and the

oxygen-helium mixtures and therefore was stated in terms of Graham's Law. The fact that helium has a slightly greater viscosity than nitrogen, as pointed out by Barach, is not pertinent to the argument since it is the viscance or viscosity property of the system that must be considered and not the viscosity of the gas mixture.

Aside from these very minor technical criticisms the book is to be highly praised and should be recommended to every medical internist and anesthetist. An excellent bibliography is included.

Clinical Lectures on the Gall Bladder and Bile Ducts. By Samuel Weiss. Pp. 320. (\$5.50). Chicago, The Yearbook Publishers Inc., 1944.

The accumulated experiences of long work in the diagnosis of abnormal biliary conditions has gone into the preparation of this book. On the whole, it is fairly well written by a man who certainly can speak authoritatively on the subject. The gall bladder and the associated ducts are discussed from the viewpoint of their most common diseases and the diagnosis, clinical and laboratory procedures and therapy are presented. Various aspects are evenly balanced so that few details are overemphasized at the expense of others.

Certain opinions are expressed which may not find agreement. However, the reasons for these usually are sound. A particularly questionable procedure is the lavage of the stomach with what appears to be a mixture of most of the astringents listed in the *Pharmacopeia*. A selected bibliography of medical periodic literature during the past ten years is included. Typographic errors are few. The book should be of interest to the internist and gastroenterologist.

Tropical Nursing. By A. L. Gregg. 2nd Edit., Pp. 185. (\$3.00). New York, The Philosophical Library, 1944.

The subtitle of this book is "A Handbook for Nurses and Others Going Abroad". In itself this small book may not be wholly adequate for the beginner but for the nurse who has had nursing experience in temperate countries, the information contained here should prove very helpful.

The diagnosis, treatment, and prophylaxis of most of the commonest diseases likely to be encountered in the tropics are discussed briefly and clearly. A brief section is devoted to the care and treatment of the eye in the tropics. Included are various techniques and advice, such as those about giving blood transfusion, disposal of the dead, and preparation of turpentine stupes. A short glossary of terms employed is included.

A Textbook of Biochemistry for Students of Medicine and Science. By A. T. Cameron. 6th Edit. Pp. 376. (\$4.00), New York, The Macmillan Co., 1942.

This textbook by Professor Cameron was first published in 1928. Since then several of the subsequent editions were in sufficient demand to require reprintings. There are also editions in Spanish and Chinese.

The publication of the present edition owes much to the might of the British and American Navies since the book was printed in Great Britain and the author is Professor of Biochemistry in the Medical School of the University of Manitoba, Canada. The effects of the war are seen in the somewhat poor quality of the paper used.

The material is well presented and the book is adequate for the purpose intended. However, the sections dealing with the digestive system are somewhat out of date. Thus the theory of acid control of the pylorus is presented without mention of later work which invalidates it. The statement that secretin stimulates bile flow from the liver is open to question: it is well known that most secretin preparations contain impurities which might well have choleric effects. A statement that the gastric juice of infants is only very slightly acid is not in keeping with the findings of several recent investigators. The specific gravity of pancreatic juice is given as having an average value of 1.007. This very likely is erroneous since a solution of bicarbonate isosmotic with pancreatic juice (and blood) has a specific gravity not far below this figure. Addition of enzymes to the sample contribute further to its weight. The specific gravity of secretions depends entirely on how they are collected and on the type of stimulus used to obtain the secretion. Thus in the dog pure pancreatic juice obtained from the pancreatic duct may vary in specific gravity from about 1.008 to about 1.030, depending on the stimulus operating at the time. The illustrations are useful tho their reproduction is none too clear, probably because of the poor paper. However, figure 6, showing the approximate position and size of the endocrine glands in relation to other organs, would appear to be out of place in this book.

The chapters on an Introduction to Pharmacology and on Immunochemistry are well written as are also most of the other chapters with the exception of the sections indicated above. The student should certainly know medical biochemistry after studying this book.

Virus Diseases in Man, Animal and Plant. By Gustav Seiffert. Translated by Marion Lee Taylor. Pp. 332, (\$5.00), New York, Philosophical Library, Inc., 1944.

"By the term 'virus' are designated substances that can engender definite contagious diseases whose nature and character are not yet clearly known. In this sense virus means somewhat the same as the old concept 'contagium'. Through the discoveries of bacteriology and protozoology, what was formerly understood by contagium has been replaced by definitely known and biologically identifiable stimuli. The rest of the pathogenic stimuli have shrivelled to the group of *vira*, in which biological research has for a long time been imperfect through lack of proper methods, but possibly just because of that they seem to stand in closer relationship to one another or possess very similar characteristics. *Virus* is not a scientifically founded biological idea, as has been believed, but only a collective designation imposed by methods. It has been introduced everywhere, conditioned especially by a similar technique or virus identification. It is possible that today the term virus has a biologically founded content in so far as all

vira can be regarded even systematically as closely related. But it is just as probable that the *vira* are divided into groups remote from one another systematically, whether they are microorganisms, substances resembling enzymes, lifeless substances, or the like."

It is with these statements that Seiffert begins his book on virus diseases. His pointing out that "the rest of the pathogenic stimuli have shrivelled into the group of *vira*" impressed us most favorably. The literature abounds with reports of diseases credited by the various authors to a virus though no positive evidences to support their claim are presented. There is no indication at present that this careless practice is decreasing and so we welcome a book which in its opening lines presents this unfortunate practice in its proper light. In considering the problem of influenza it is emphasized that all cases reported as influenza cannot be accepted as a "uniform sickness". These and other statements we accept as presenting the author's sound appreciation of the problems of virus study.

The reader's realization of what appears to represent the worthiness of the author serves only to heighten the impossible translation of the book. A less literal translation would have made easier reading. Typographical errors are numerous. Some of the errors are no doubt due to the difficulties in publishing a book during wartime. However, the book is an excellent source of references to the European literature and is well worth reading by all interested in *vira* and virus diseases.

A Textbook of Medicine by American Authors Edit. by R. L. Cecil. 6th Edit., Pp. 1566, (\$9.50), Philadelphia, W. B. Saunders Co., 1943.

After reading this textbook written by a group of 154 collaborators, it becomes clear that the days are probably past when a single individual could write authoritatively on the various phases of medicine. Professor Cecil is to be congratulated for his selection of contributors, each of whom has specialized in the field he writes about.

The sixth edition of this textbook should be well received by the practitioner and the appreciative medical student. During the seventeen years that have passed since publication of the first edition, Cecil's Medicine has gained a wide popularity. Contributing to its popularity are the clarity and conciseness of description and authority of presentation. This book will certainly remain a standard text for years.

Twelve new articles appear in this edition for the first time. Among these are virus pneumonia, contact dermatitis, rheumatic heart disease and senile osteoporosis. War conditions and military medicine show up in such articles as undernutrition, aviation medicine, motion sickness and shock. Several new introductory chapters have also been added, covering Rickettsial diseases, pneumococcal infections, metabolic diseases, disease of the digestive system, blood diseases, cardiovascular diseases, deficiency diseases, and endocrine diseases. In addition to other changes, thirty-one of the topics have been completely rewritten.

The format of the present edition has been changed

from single to double column pages. This is a real improvement since it is well known that the eye can follow short lines more readily and with less fatigue than it can long lines. Illustrations are few in relation to the number of pages but they have been well chosen.

The book is well indexed, as indeed such a book must be if it is to serve its function as a handy reference volume. A table of normal values for the commoner laboratory tests should be of help to both student and physician.

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CLINICAL MEDICINE

STOMACH

GARDNER, H.: *Diaphragmatic hernia with torsion of the stomach and acute obstruction.* (Brit. Med. J., No. 4359, P. 114, July 22, 1944.)

The case record of a 57 year old woman is presented. At operation the stomach was found twisted and enormously distended (18 to 20 inches long, 8 to 9 inches in diameter). In spite of the excessive stretching of the muscularis and the mucosa, gastric function returned rapidly. The diaphragm opening which was to the left of the oesophagus, was closed by double catgut sutures. The patient was still well 6 months after operation.—F. E. St. George.

MORRIS, H. H.: *End results in the surgical treatment of gastric carcinoma.* (New Orleans Med. Surg. J., V. 96, P. 254, Dec., 1943.)

Altho a larger percentage of the total admissions of patients with gastric cancer is now being treated surgically than in the past, the mortality rate is dropping significantly. Of 758 patients treated at the New Orleans Charity Hospital from 1922 to 1931 inclusive, 32.3 per cent died. Of 533 not operated upon, 70.3 per cent died. Analysis of 200 surgical cases during this period showed 51.4 per cent mortality following gastrectomy, 30.4 per cent following exploration and 43.6 per cent following palliative procedures.

From 1932 to 1940 inclusive, 1,163 patients were treated for gastric cancer. Of 829 patients not treated, 218 died in the hospital; of 344 patients operated on, 138 died in the hospital. Analysis of 200 surgical cases during this period showed mortality rate following gastrectomy to be 56 per cent, exploration 23.5 per cent and palliative measures 48 per cent.

In a series covering the last two years, 105 were males while 50 were females. More than three-quarters of the cases were in the fifth and sixth decade. The younger patients seemed to present a more fulminating type of cancer.—Wm. D. Beamer.

ROSSETT, N. E. AND FLEXNER, J.: *The effect of certain antacids in man measured by a simplified method for the continuous recording of gastric pH.* (Ann. Int. Med., V. 21, P. 119, July, 1944.)

A method is outlined for the continuous recording of gastric pH in the human. When patients were given milk to which calcium carbonate had been added, it was found that the calcium carbonate aided the buffering powers of the milk and the milk prevented the calcium carbonate from causing an excessive rise in pH. The effect of this mixture was prolonged as was the effect of the mixture of milk of magnesia and colloidal aluminum hydroxide. The latter mixture overcomes the constipating effects of aluminum hydroxide and also overcomes the initial rise in pH which has been found when milk of magnesia is given alone.—R. L. Burdick.

BOWEL

BERKLEY, W. L. AND WATKINS, H. C.: *Prophylactic use of sulfathiazole in appendicitis.* U. S. Naval Med. Bull., V. 42, P. 1, Jan. 1944.)

Cases of abdominal complaints aboard a Naval transport were studied closely with the view of picking out those suggestive of acute appendicitis. This resulted in the diagnosis of acute appendicitis in eight men. All eight were given sulfathiazole, two grams in the first dose and one gram every four hours thereafter. Liquids by mouth were allowed. Pain, tenderness, and rigidity regressed after twelve hours. It is believed that this form of therapy should prove valuable in either averting the acute stages of appendicitis or in keeping the condition quiescent until a more favorable time for operation arrives.—G. Klenner.

FIGARRA, B. J. AND DEGEN, W. B.: *Congenital atresia of the ileum, spontaneous perforation and multiple*

intussusception. (*Am. J. Surg.*, V. 65, P. 123, July, 1944.)

Congenital atresia of the ileum is seen infrequently. A case is reported in a premature infant in which there was spontaneous intestinal perforation. Signs of intestinal obstruction were evident 24 hours after birth. Because of wide-spread peritonitis, surgical intervention was unsuccessful.

A twenty-three month old male child had a double intussusception with symptoms of twelve days standing before surgery was attempted. The terminal ileum was invaginated in the cecum and the cecum in turn was invaginated in the ascending colon. The appendix was also drawn into the colon. The intussusception was reduced in the orthodox fashion. Recovery was uneventful.—I. M. Theone.

SUTHERLAND, P. S. AND BERGER, F. M.: *Milk-borne gastro-enteritis due to Salmonella dublin.* (*British Med. J.*, P. 488, April 8, 1944.)

A fairly extensive outbreak of diarrhea was found to be due to milk, because everyone sick was supplied with milk from a single farm. In addition, a small proportion of the cases suffered a profuse herpetic eruption on the lips and nose.

From the various examinations made by the investigators and the precautions instituted by them it appeared that the cows were the source of the causative organisms. These had been isolated from cases and identified as *Salmonella dublin*. A few of the herd were suffering from cowpox, but otherwise they all appeared to be healthy. Under the existing conditions it was impractical to collect specimens of dung and blood from each member of the herd, so that milk was examined. Cultures were negative, but when the milk was treated with rennet and the whey tested for antibodies one cow was found to have a high titer. Later examination of the dung of this cow gave almost pure cultures of *S. dublin*. The cow was a carrier.—George P. Blundell

LITVAK, A. M. AND LEVY, H.: *Nonspecific ulcerative colitis in childhood. case report and review of literature.* (*Arch. Pediat.*, V. 61, P. 293, June 1944.)

Altho relatively uncommon, chronic idiopathic ulcerative colitis is probably more frequent than is generally recognized. The condition may present itself by insidious onset and in various forms. The picture varies in almost every case and the course of the disease is unpredictable. Diagnosis is frequently made only by exclusion of other diseases. The literature shows the disease may occur at any age, tho older children are more frequently the subjects. It occurs more frequently in males than females. It rarely follows infections but is most frequent in those months in which upper respiratory infections are most common. The fulminating form is more frequently seen in children than in adults.

Polypsis of the colon and carcinoma have been recorded complications. The etiologic agent is unknown

tho a specific diplostreptococcus has been suspected. Avitaminoses and nutritional disturbances have also been blamed as primary factors. The pathologic process is believed by Bruce and Barger to be initiated by capillary thrombosis of the colon. Treatment is not specific; a great number of drugs have been tried without success. High vitamin diets, elimination diet, kaolin, vaccines, antidysentery serum and other therapies have been used with varying results. The results of surgery have likewise been inconclusive. Mortality has been 23 per cent. A case is reported in which chiniofon was believed to be beneficial.—F. X. Chockley.

REIMANN, H. A., PRICE, A. H. AND HODGINS, J. H.: *Negative results in studies of epidemic diarrhea, nausea and vomiting of unknown cause.* (*Proc. Soc. Exp. Biol. and Med.*, V. 55, P. 233, May, 1944.)

The report is concerned with the manipulations of specimens obtained from medical students who had been patients during an outbreak of epidemic nausea, vomiting and diarrhea. Twenty per cent of the student body were affected. This syndrome was not defined or characterized. Ten patients were examined for bacteria associated with enteritis; both their stools and pharyngeal secretions were negative. Five patients provided specimens which were examined for the presence of a virus by inoculating mice orally, intranasally, rectally and intracerebrally. Three of these five specimens were inoculated onto the chorio-allantoic membrane of the developing chick embryo. Eight stool specimens were inoculated intranasally into 8 four-week-old calves. One calf died a month later. No filtrable infectious agent was isolated from any of the cases examined.—G. P. Blundell.

DOCKERTY, M. B., ASHBURN, F. S., AND WAUGH, J. M.: *Metastasizing carcinoids of the ileum.* (*Proc. Staff Meet. Mayo Clinic.* 19, 228, May 3, 1944.)

Report of thirteen cases of metastasizing carcinoid tumors is made. Previous literature refers to the carcinoids as benign, clinically silent, generally native to the tip of the appendix and occurring as solitary tumors. In contrast, these thirteen cases all showed metastasis either at operation or necropsy, resulted in major gastrointestinal complaints, involved the ileum primarily, and presented multiple primary nodules.

Carcinoid tumors arise from intestinal crypts and the authors suggest they are entodermal or glandular in origin. They are malignant irrespective of location; usually they are single and rarely spread in the appendix but in the ileum are frequently multiple with metastasis (one-third of the cases), and they are not clinically silent when originating in the ileum. Since the histogenesis, mode of growth, rate of spread and response to treatment of carcinoids differ from other types of adenocarcinoma, grade I, it is recommended that they be reclassified, removing them from the category of benign neoplasms.—J. R. Peaver.

FRANKMAN, W.: *The therapy and the basic principles of varicose symptom complex recti.* (*Med. Record*, V. 157, P. 215, Apr. 1944.)

"Hemorrhoids are caused by a disturbance of the portal circulation whereby a damming back of the blood is brought about, causing dilatation of the rectal veins, or hemorrhoids. . . . This principle explains simply and scientifically the causes of pruritus ani, scorti and vulvae." The portal blood is dammed back and so fails to reach the liver to be detoxified. The toxin is then able to cause the pruritus. Anal fissures and fistulas may result for the same reason from the same cause. Fissures do not heal slowly due to the action of the anal sphincter because fissures may occur above the sphincter muscle. The fissure is really a ruptured thrombotic vein. A technique is presented for treatment of hemorrhoids which is based on the principle outline. Essentially it is an injection procedure, using a specially devised proctoscope with syringe attached to deliver controlled amounts of injection fluid. The site and conditions for injection are outlined and eight case histories are given.—D. A. Wocker.

ALVAREZ, W. C., AND BARGEN, J. A.: *The value of the blood sedimentation rate in recognizing diarrheas due to organic disease.* (*Proc. Staff Meet. Mayo Clinic*, 19, P. 255, May 17, 1944.)

The importance of the blood sedimentation rate should be emphasized in differentiating between functional diarrhea (low rate) and organic disturbances in the bowel, e.g., regional stenosing enteritis, beginning ulcerative colitis, tuberculous or cancerous lesion, or bacillary dysentery (high rate—40 or 50 mm. per hour). The blood sedimentation rate also helps in estimating the extent and seriousness of thrombo-vascular colitis: the rate may be normal if only the rectum and sigmoid are involved.—E. R. Feaver.

GOODE, T. V., NEWBERN, W. R.: *Intestinal obstruction associated with defects in the broad ligaments of the uterus.* (*Review of literature and case report Am. J. Surg.*, V. 45, P. 127, July, 1944.)

The authors present a case of intestinal obstruction due to a defect in the broad ligament. Strangulation and protrusion through the broad ligaments of the uterus are rare, only 27 cases having been reported in the literature. Nine of these cases occurred in those having had Baldy-Webster operations. They are not true hernias, rather protrusion through defects in the broad ligament. These defects may be congenital, or may be due to repeated mild trauma. Those not resulting from previous surgery occur in the region of the mesosalpinx. The diagnosis is quite difficult to make when partial intestinal obstruction occurs. With complete intestinal obstruction occurring in a multipara with a mass in the region of the broad ligament and a negative history for acute pelvic inflammatory disease, then the diagnosis is likely. Treat-

ment is always surgical and early, and when repairing the defects in the broad ligament, none-absorbable suture material should be used.—J. Bernard Bernstein.

LIVER AND GALLBLADDER

WILLARD, J. H.: *Acute infectious jaundice.* (*U. S. Nav. Med. Bull.*, V. 42, P. 1085, May 1944.)

Acute infectious jaundice accounted for more than 750 admissions to the author's base hospital during a 6-month period. The mortality rate was nil, but the average patient was not ready for duty within 6 weeks. The peak of admissions was in April 1943. The incidence of jaundice did not parallel that of other infections and no correlation could be made except that recurrent malaria or gastro-enteritis seemed to increase susceptibility and favor the severity of the course. A prodromal course of several days of anorexia, malaise, nausea, fever, vomitis and diarrhea usually preceded the clinical jaundice. Typically, all symptoms including upper abdominal soreness would begin to subside in about 2 weeks but others ran a much shorter or a longer course. The liver was not usually large nor was the spleen. Malaria may have been a factor in cases of enlargement of these organs. Other diseases such as Weil's jaundice have apparently been ruled out. Many of the patients were evacuated early and could not be followed. The absence of complications in these cases seems to be evidence against a bacteriologic etiology.—Wm. D. Beamer.

MACLAGAN, N. F.: *The serum colloidal gold reaction as a liver function test.* (*Brit. J. Exp. Path.*, V. 25, P. 15, Feb., 1944.)

The serum colloidal gold test gave positive results in 100 per cent of cases of liver cirrhosis and in a high percentage of cases with generalized liver diseases. Normal subjects gave positive results in 10 per cent of the cases. The reaction and ionic strength of the medium greatly influence the results. The procedure was modified by introducing a buffer solution which permits carrying out the test in a single tube without preliminary standardization of the gold sol. The test is valuable in indicating the presence of liver damage and in distinguishing between hepatic cirrhosis or infective hepatitis and obstructive jaundice. Cases of arsenical jaundice (40 per cent positive) gave different results from infective hepatitis (95 per cent positive), suggesting some pathological difference between the two groups.—N. M. Small.

POST, J. AND PATEK, ARTHUR J., JR. *Serum proteins in relation to liver disorders.* (*Bull. New York Acad. Med.*, V. 19, P. 815, 1943.)

Evidence has been reviewed which indicates the liver as the probable site of formation of blood albumin, fibrinogen and prothrombin. In acute liver disease the fibrinogen and prothrombin levels of the blood may be reduced. The albumin may show slight reduction and the globulin moderate elevation. In more severe

forms of acute liver disease these changes may be pronounced. In chronic liver disease, notably, cirrhosis of the liver, the serum generally is reduced, whereas the serum globulin is normal or increased. The degree of reduction in the albumin level seems to be correlated with the prognosis as to duration of life, clinical course of the disease, and with the appearance and disappearance of ascites. Nitrogen balance studies in cirrhosis of the liver show that patients with this disease can absorb and retain protein, but that there is an apparent defect in synthesis of serum albumin.—Biological Abstracts.

ULCER

GILL, A. M.: *The treatment of peptic ulcer in wartime.* (Med. Press. Circ., V. 1, P. 84, 1944.)

Few cases of peptic ulcer will not respond to medical treatment alone if properly handled. Treatment depends chiefly upon the accurate diagnosis of the condition. The cardinal features of gastric ulcer and duodenal ulcer are presented. Treatment is based on the principles of rest, neutralization of free acid, and inactivation of pepsin. Bed rest is for a period of 4 to 6 weeks, and mental rest at all times is essential. Return to activity is only permitted in gradual stages. The patient should be told the rationale for the treatment so that he will understand why his cooperation is absolutely necessary. Reduction of gastric acidity is by means of antacids and drugs. Diet is of utmost importance and should be such as to assure continuous neutralization of the acid. Overdistension and flatulence is avoided by meals of small bulk. All the essential vitamins are included. Aluminum hydroxide and belladonna are given before bedtime to the patient who still complains of pain. Iron must be given for the anemia or hemorrhage.

The diet should be adhered to for at least two years. At no time should more than two hours elapse between meals; biscuits, etc. serve to bind the acid. Smoking after a meal and small amounts of alcohol during a meal are permitted. Strong purgatives must never be used.

Surgical intervention should be permitted only when all reasonable medical care has failed to relieve the patient and also in cases of perforation, stenosis, obstruction and malignancy.—D. A. Wocker.

PAPPWORTH, M. H. AND LOUTIT, J. F.: *Gastro-duodenal hemorrhage treated medically with cathusiastic blood transfusion.* (Lancet, V. 2, P. 469, Oct. 16, 1943.)

Hematemesis was regarded as severe if hemorrhage occurred more than once, or if occurring only once there were also signs of shock. Of 30 cases of hemorrhage of the stomach and duodenum treated by transfusion, only one death occurred. Cases with signs of shock were transfused rapidly to prevent the irreversible changes to tissues which are known to be produced by shock. Subjects not in shock but showing hemorrhagic anemia were transfused to both correct the anemia and insure

against the possibility of further hemorrhage. Transfusion of all cases showing a hemoglobin below 60 per cent is recommended. Persistent bleeders do best with the constant intravenous drip, one and one-half to two liters or more per day. Transfusions with whole blood or concentrated red-cell suspensions are advised.—F. E. St. George.

THERAPEUTICS

PETERSON, O. L., DEUTSCH, E. AND FINLAND, M.: *Therapy with sulfonamide compounds for patients with damage to the liver.* (Arch. Int. Med., 72, 594, Nov. 1943.)

The authors report on a series of 37 patients who presented acute or chronic damage to the liver and who, for various reasons, had received sulfathiazole and/or sulfadiazine in full therapeutic doses. In each of these cases some studies were made in an attempt to determine the effect of the sulfonamide therapy on hepatic function as measured by hippuric acid, prothrombin time, and bromsulfalein excretion tests.

Thirteen cases with acute hepatitis associated with bacterial infections, including seven patients with hepatitis secondary to severe lobar pneumonia, upon sulfonamide therapy showed an improvement in hepatic function which followed improvement in the underlying infection. In the above-mentioned seven patients, the jaundice was completely cleared.

Twenty-four patients with chronic disease seemed to tolerate the drugs well. Eleven patients showed no apparent change in the status of the liver although infection in most was favorably influenced by sulfonamide therapy. Eleven other patients showed definite improvement in hepatic function concomitant with clearing up of the infection for which the drugs were given. In the two remaining cases there was some temporary aggravation of hepatic dysfunction during chemo-therapy at a time when they were manifesting other toxic reactions to the drugs.

The toxic effects of sulfonamide therapy were most frequently observed in patients with portal cirrhosis and were encountered most frequently with sulfathiazole as against the sulfadiazine therapy. The authors conclude that in presence of damage to liver as in cases of acute hepatitis, sulfathiazole or sulfadiazine need not be withheld when their use is otherwise indicated—with sulfadiazine being choice drug. However, caution is warranted in the administration of sulfonamides to patients with severe portal (Laennec's) cirrhosis of liver.—H. Siplet.

STAFFORD, C. E., BESWICK, J., AND DEEB, P. H.: *Evaluation of sulfonamides in treatment of peritonitis of appendical origin: a review of 903 cases of acute perforative appendicitis.* (Am. J. Surg., V. 64, P. 227, May 1944.)

The authors review 903 consecutive cases of acute appendicitis with either rupture or abscess. The four year period, 1939-42, showed a mortality rate due to perforation of 3.4 per cent. This is a decrease

from the previous mortality rate of 9.2 per cent. During the 1942 period about 98 per cent of the cases received chemotherapy; the decrease in mortality rate is attributed to the increased use of sulfonamides. Drainage by tube has also become less frequent since sulfonamide therapy has been inaugurated. Intraperitoneal implantation of the sulfa drug early following perforation of the appendix has proven to be very beneficial in combating peritonitis. Appendectomy in cases of appendical abscesses was found possible with sulfonamide therapy.—F. X. Chockley.

HUGHES, WM.: *Treatment of some complications of bacillary dysentery.* (*British Med. J.* No. 4350, P. 697, May 20, 1944.)

The following drawbacks to the use of sulphaguanidine in the treatment of bacillary dysentery have been recognized: (1) the drug is expensive, (2) a large dose is required, and (3) as an oral remedy, vomiting often makes it impossible to use.

Sulphapyridine is cheap and its soluble salt is available. It has been given intravenously in adults and intramuscularly into the scapular muscles in children whenever injection was indicated. The cases encountered were often complicated by nutritional deficiencies of the vitamin B₁ complex. Milk was given once the sulphonamide therapy was established to supply fluids and to meet nutritional deficiencies.

It was stated that in complicated cases the combined therapy met very well the theoretical expectations.—G. P. Blundell.

SURGERY

HOGARTH, J. B.: *A modification of the invagination method of intestinal anastomosis.* (*Brit. Med. J.*, No. 4358, P. 75, July 15, 1944.)

"The mesenteric attachments are ligated and divided close to the bowel. . . . on each side of the diseased portion for a distance of one and a half to two inches two portions of healthy bowel adjacent to the diseased are crushed." The diseased region is then occluded by silk rather than catgut sutures and the healthy bowel portions approximated. By means of a special corkscrew, one end of the bowel is made to invaginate into the other, and the invagination is carried to the point where the whole diseased portion is now buried within the healthy segment. The approximated bowel ends are drawn together by interrupted sutures. A St. Thomson angle forceps is inserted thru the bowel wall and pushed thru the double diaphragm formed by the diseased bowel segment. The opening made by the forceps is closed by a pursestring. This type of "aseptic" operation has been used successfully on three patients whose case records are presented.—F. E. St. George.

HICKEN, N. F., CORAY, Q. B. AND CARLQUIST, J. H.: *A new technique for using the Levine tube in biliary intestinal anastomoses.* (*Surg. Gyne. Obstet.*, V. 78, P. 58, 1944.)

Just before operation a sterile Levine tube is passed into the stomach. When the operation is to be a cholecystogastrostomy, the tip of the Levine tube is brought out thru the gastric incision and inserted into the gall bladder. Chromic catgut sutures prevent the tube-tip from slipping back into the stomach. This permits drainage of the gall bladder into the stomach and maintenance of a functional biliary anastomoses.

If the operation to be performed is a choledochenterostomy, the tip of the Levine tube is brought out thru the pylorus. It is then inserted either into the common bile duct or into the gall bladder. Anastomosis between the biliary segment involved and the intestine can be made easily around the indwelling Levine tube. Post operative occlusion of the stoma due to edema, fusion, etc. is less common with the tube in place. When the biliary tree has regained its normal size, the tube may be removed.—G. Klenner.

PICKRELL, K. L. AND CLAY, R. C.: *Lobectomy of the liver.* (*Arch. Surg.*, V. 48, P. 267, 1944.)

Total excision of the left lobe of the liver has been recorded only twice tho partial excisions have been reported frequently. The authors successfully performed complete resection of the left lobe in three cases (for carcinoma, haemangioma and gumma). Two difficulties of liver resection are the extensive hemorrhage of a tissue that retains sutures poorly and the possibility of upsetting liver function. The latter difficulty is not as dangerous as was once thought, but the former difficulty still exists. The authors describe their technique which is relatively bloodless.—N. M. Small.

EXPERIMENTAL MEDICINE

PATHOLOGY

WIERDA, J. L.: *Diverticula of the colon in rats fed a high fat diet.* (*Arch. Path.*, V. 36, P. 621, Dec., 1943.)

It has been supposed that diverticula of the colon is restricted only to man and that it occurs only in the latter half of the life span.

Three rats were fed a high fat diet for ninety to one hundred and eleven weeks. One or more diverticula of the colon developed in each. In appearance the diverticula resembled that found in humans, and seemed to be the result of high pressure within the intestine acting against a specific limited area of the wall. The pattern or size of the blood vessels did not lead to the belief that these might play a part in the anomaly. The regularity of the position of the diverticula and the similarity of the walls seem to indicate that for unknown reasons they were developed in response to the high fat diet.—M. H. F. Friedman.

PATHOLOGICAL CHEMISTRY

VILLELA, GILBERTO G.: *Action of anti-toxic extracts of the liver on the level of hepatic glutathione in experimental poisonings.* (*Rev. Brasil. Biol.* 3, P. 99, 1943.)

Experimental poisoning of mice with carbon tetrachloride and neo-arsphenamine decreased the total glutathione of the liver. Liver anti-toxic extracts protected mice which were injected with the toxic substances, and maintained total glutathione at about normal. Technic of the experiments and methods of determining glutathione are described.—Courtesy Biological Abstracts.

YOUNG, R. M. AND RETTGER, L. F.: *Decomposition of vitamin C by intestinal bacteria.* (*J. Bacteriol.*, V. 46, P. 351, Oct. 1943.)

The serious effects of vitamin C loss from the body are well known. It therefore is of importance to learn whether, in spite of adequate vitamin C intake, any of the vitamin C is lost to the body for purposes of utilization, by bacteria within the intestine. The present study supports other findings that vitamin C deficiency may indeed result in this manner. This is particularly true when there is an extra need for vitamin C and reserve depots have been exhausted. Ascorbic acid was found to be utilized readily by bacteria if the culture medium contained peptone or other organic nitrogenous substances but was protected from destruction if the culture medium contained a readily fermentable carbohydrate such as dextrose.—N. M. Short.

SAXTON, JOHN. A. JR., AND MILLER, MARY L.: *Relation of the postmortem interval to the synthesis of glycogen from dextrose by surviving liver.* (*Arch. Pathol.*, 37, P. 34, 1944.)

The ability of surviving slices of rabbit liver to synthesize glycogen from dextrose when incubated in a medium comparable to intracellular fluid decreased rapidly after death. Glycogenesis was not consistently demonstrated if fifteen or more minutes elapsed post-mortem before the tissues were removed from the animal. A relatively high initial level of glycogen in the liver seemed to inhibit glycogenesis in vitro. This method of study is not generally applicable to human liver tissue in disease, because tissue can rarely be obtained from the cadaver during the first few minutes postmortem and because a high initial glycogen content of the liver may be expected to inhibit further glycogenesis in vitro. A correlation of the glycogen content of the human liver postmortem with the amount of carbohydrate available to the liver during life is suggested as a more suitable approach to the study of this phase of liver function in human disease.—Courtesy Biological Abstracts.

FOSDICK, L. S. AND RAPP, G. W.: *The effect of proteolytic enzymes on acid formation in the mouth.* (*J. Dental Res.*, V. 23, P. 81, April, 1944.)

Saliva was collected by paraffin stimulation (chewing). Calcium determinations were run on a portion

of fresh saliva for controls. To other portions were added glucose, powdered human tooth enamel, and the test material. After a 4 hour period of incubation, calcium determinations were done on all samples. Proteolytic enzymes were used in an attempt to break down the enzymes which cause acid formation in the mouth. Test materials used were papain, trypsin, and pancreatin. It was found that trypsin and papain stimulate acid formation while pancreatin has no effect.—R. L. Burdick.

MISCELLANEOUS

HUBBARD, R. S. AND JEWETT, M. K.: *Note on the clarification of bile.* (*Am. J. Clin. Pathol.*, V. 14, P. 53, May, 1944.)

Four methods are given for the clarification of bile obtained from humans thru a "T" tube established at operation. The methods are inadequate for good clearing when the bile is thick, as when it is obtained from the gall bladder by intubation. One of the methods was found useful in sugar determinations even in samples in which the concentration of sugar was small.—L. R. Burdick.

DIAZ-RIVERA, R. S. AND RASPBERRY, E. A.: *Amebiasis Analytical study of cases admitted to a Philadelphia hospital during the last 5 decades.* (*Am. J. Med. Sci.*, V. 207, P. 754, June, 1944.)

The estimated incidence of amebiasis in the United States is 20%. The actually diagnosed incidence has varied from 1.9% to 11.3% in Philadelphia. During the last 5 years, of 61,574 medical admissions to the Hospital of the University of Pennsylvania, only 32 were diagnosed as amebic dysentery. Of 122,933 surgical admissions, only one of 5,233 deaths was due to amebic hepatic abscess. This study is based on twenty-five complete records, the remainder being discarded because of insufficient data. Sixteen patients acquired the disease prior to 1933, 9 after that year. Only 4 of the 16 acquired the disease in this country. Of the 9 cases, 2 had acquired it at the Chicago World's Fair, and one in Poland. In all, at most 7 cases had apparently acquired the disease in or nearby Pennsylvania, and 5 of these were admitted in the past 6 months. In 22 of the cases, the vegetative form was found in the feces; in 2, the cystic forms, and in the remaining case, motile amebae were found in the pus of the hepatic abscess. Of 14 proctoscoped cases, 10 had ulcerative rectosigmoiditis, 2 had catarrhal inflammation, and 2 had normal mucosa. Eleven cases had leukocytosis, and 9 had an eosinophilia. There were 2 deaths, one from bowel perforation, the other from the hepatic abscess. The effect of treatment is uncertain. It is thought that high index of suspicion and examination by competent parasitologists will raise the diagnostic percentage.—Wm. D. Beamer.

Proceedings of the New York Diabetes Association — February 1944

February 19, 1944

"Report of Diabetes Surveys in Philadelphia"

..... Joseph T. Beardwood, Jr., M.D., Philadelphia, Penna.

"Normal Standards in the Treatment of Young Diabetics"

..... Joseph H. Barach, M.D., Pittsburgh, Penna.

Diabetes-Round Table Discussion

Cecil Striker, M.D., Elliott P. Joslin, M.D.,
Cincinnati, Ohio Boston, Mass.

Seale Harris, M.D., Howard F. Root, M.D.,
Birmingham, Ala. Boston, Mass.

J. West Mitchell, M.D., Edward S. Dillou, M.D.,
Pittsburgh, Penna. Philadelphia, Penna.

Proceedings of the New York Diabetes Association
—Open Meeting held at the New York Academy of
Medicine on the evening of February 19th, 1944.

Dr. George E. Anderson, President of the New York
Diabetes Association, Inc. and Chairman of the Com-
mittee on Internal Medicine, presiding.

Dr. Anderson:

THIS evening's scientific session is being sponsored
by the Committee on Internal Medicine of the New
York Diabetes Association. We are most fortunate in
having on the program an array of talent in the field
of diabetes such as is only rarely assembled except in
major convention. The New York Diabetes Association
has, as it were, commandeered en masse the ex-
ecutive council of the American Diabetes Association
which this day met in New York City. I am honored
and privileged to greet our distinguished guests, two
of whom will read papers, all of whom will take part
in formal round-table discussion on diabetes.

The first paper of the evening will be presented by
one who is so well known to the New York audiences
as to require little introduction, Dr. Joseph T. Beard-
wood, Jr. of Philadelphia, President incumbent of the
American Diabetes Association.

"Report of Diabetes Surveys in Philadelphia,"

Joseph T. Beardwood, Jr., M.D.

It is my object tonight to present the results of sev-
eral attempts to survey the diabetic situation in Phila-
delphia and to ascertain if possible, the total number
of diabetics in the city and to break down the actual
causes of death in those persons in whom diabetes was
mentioned on the death certificate.

This latter work has been carried out for the last
three years by a sub-committee on diabetes mortality
of the Diabetic Committee of the Philadelphia County
Medical Society. Dr. Roland S. Snader is Chairman
of the Diabetic Committee and by his courtesy the
speaker, who is chairman of the sub-committee, is able
to present this report. There were no monies avail-
able for this study and it was carried out with the
clerical aid of the office force of the Philadelphia
County Medical Society and the members of this Com-
mittee. Through the cooperation of Dr. Hubley Owen,

Submitted, March 21, 1944

Director of Public Health, a copy of all death certi-
ficates on which diabetes was mentioned was sent to the
County Medical Society together with the name of the
physician signing the death certificate. A questionnaire
was then sent to the physician. This questionnaire
inquired as to the age of the patient, duration of dia-
betes, number of children, previous diabetic treatment
—particularly as to whether qualitative or quantita-
tive diets had been used, whether insulin had been
taken, whether the diabetes had been adequately con-
trolled before death, and the physician's interpretation
of the actual cause of death—inquiring particularly as
to urine and blood chemistry studies immediately ante
mortem.

In many instances the questionnaire was the only
data that we had to go on. In some cases personal
inquiry was made and further follow-up was done.
Some of these deaths occurred in institutions where
members of the committee were on the staff and con-
sequently the original questionnaire could be amplified.

We think our greatest disappointment was in the
attempt to find out if these people had been adequately
treated for their diabetes before their last illness. The
information so secured was most inadequate, and the
answers of many physicians, particularly concerning
patients who had no clinic care, emphasized again and
again that the patient's diabetes could not be controlled
because "they would not adhere to diet", "refused to
take insulin", "family refused to cooperate". It was
interesting to note that these comments were very
rarely made concerning patients who were attending
clinic or had been standardized in hospitals, and the
Committee felt very definitely that in many cases the
lack of cooperation on the part of the patient was
probably due more to a lack of appreciation on their
part, and in many instances on the part of their physi-
cians, of the methods of handling diabetes and that if
intelligent diabetic education could have been insti-
tuted, their cooperation would definitely have been
improved.

In the years 1940, 1941 and 1942, 2499 patients
died in Philadelphia; on their death certificates ap-
peared the word "diabetes". Of these, 53 were either
coroner's cases or the information given was so indefi-
nite that questionnaires were not sent. However, 2446
questionnaires were sent out and we received reports
on 1768 of these, an average of 71.8%. After careful
analysis, it was felt that insufficient data had been
secured on 189 questionnaires so that this analysis
represents a study of 1579 cases.

The average age at death of these patients was 64.3
years, which, interestingly enough, is the exact figure
found in the careful survey made by Dr. G. W. Lynch
of 301 deaths in Boston in 1935. In breaking this
down, we felt that 1029 (65.2%) were cases in which
diabetes, while mentioned on the death certificate, ap-
parently contributed little to the cause of death. There

were, however, 500 (34.8%) who died of diabetic complications. 362 or almost three-quarters of these patients died of diabetic acidosis, the average age at death being 55.9 years. In this group there were only 9 cases below the age of 20 and of these 7 did not know of their diabetes until admission to the hospital, and most of them died within the first 12 hours. The remainder of the group, 188 patients, died of infection in which the diabetes was uncontrolled, but they were not acidotic. We felt that probably diabetes played a contributing role in this group.

There were 276 patients who died of arteriosclerosis, 240 listed as dying of coronary artery disease, and 91 listed as having myocardial degeneration or myocarditis. From further questioning we found that many of the last group died of arteriosclerotic complications. Arteriosclerosis, therefore, accounted for 707 deaths or 44.8% as compared to Dr. Lynch's figures of 59.5%. In a little more than half of these patients we were able to obtain a history of the duration of the diabetes, which averaged 7.5 years before death.

Among the miscellaneous causes of death should be mentioned: carcinoma, which accounted for 95 deaths; tuberculosis for only 33; and uremia for 36. It is possible that some of these deaths, had more adequate chemical analyses been made, would have fallen into the acidotic group, but many of them had histories of long-standing urinary infection, which bears out the work of Root and others that diabetics stand urinary infections poorly.

The role which diabetes may have played in the production of arteriosclerosis and death in this group is, of course, a debatable one; but as their average age was in the limits when arteriosclerosis should develop even without diabetes, one hesitates to attribute a great deal of significance to the etiological significance of the diabetes. It is very interesting to us that the group as a whole has averaged just about the same in their age of death over a three-year period, i.e., 64.3 years, as compared to 58 years, which was the average age of death from all causes in the City of Philadelphia in 1942. Therefore, one might postulate that diabetics lived six years longer than non-diabetics; realizing that diabetics fall normally in the older age groups, these figures may not be too comparative.

Our impression of this study has been that in spite of its inaccuracy and its many faults, it has been well worthwhile. We have learned that a far greater percentage of diabetics die of acidosis than we previously had thought. We have also been interested in the fact that since this study was undertaken the number of cases of diabetic acidosis has shown a definite drop in each of the following two years. However, this might have been coincidental. The members of the committee have been impressed that the vast majority of patients who die of acidosis have never had the advantage of clinic instruction and care and that the education of the diabetic is of paramount importance in insuring him a life free of complications.

The committee has been somewhat amazed at the paucity and inadequacy of blood chemistry studies. Even in large hospitals many patients admitted in

acidosis have not had a CO_2 combining power done or, in our opinion, sufficient laboratory appraisal to handle the condition. We feel that in Philadelphia at least there is a tremendous amount of additional work to be done, directed mostly toward the physicians themselves to make them appreciate modern diabetic care and to have them assure their patients adequate instruction and periodic check-ups.

We attempted another survey with the aid of the Civilian Defense authorities. In Philadelphia there were organized what were called "neighborhood health groups", who during the earlier and more active days of Civilian Defense, made a house-to-house canvass inquiring as to the number of people, their ages, and any possible diseases they might have. The reason for this survey was that in event of catastrophe, the air-raid wardens would be aware of the types of people with whom they would have to deal and probably would have to evacuate from the zone. These surveys were made by committees usually consisting of a nurse or physician, so that a fairly intelligent approach was made to the problem. The Office of Civilian Defense was most cooperative. The Philadelphia Metabolic Association prepared a sheet of instructions (which was also distributed to the police and firemen) telling what diabetes is, about the symptoms of insulin reaction, and what should be done in case a diabetic is injured. After completion of the survey, in every instance when a diabetic had been found, the committee went back and gave the individual an identification disc issued by the Pennsylvania Diabetes Commission together with a leaflet of instructions stressing that it is the individual's responsibility to care for his diabetes under any and all circumstances, and that by so doing he would not become a burden on the authorities and indeed would be able to help them take care of some of the emergencies.

Unfortunately, this survey was not as thorough as had been hoped, and with the decreasing interest in the Civilian Defense activities, it is at present almost dormant. However, 34,633 people were interviewed and 357 diabetics reported. We have good reason to feel this number is conservative as many individuals had obtained employment in war industries, concealing the fact they had diabetes, and were not anxious to admit they had the disease. If we accept this figure of 357 cases, which we feel is quite conservative, it would mean that more than 1% of the population of Philadelphia are diabetic; and if projected to city-wide figures, would mean the presence of more than 19,000 diabetics in Philadelphia. If, however, we go back to the figures presented earlier that the average duration of life in a diabetic is only 7.5 years and that an average of 833 die in Philadelphia yearly, we obtain the figure of 6,047 diabetics in the city. This is a very marked discrepancy, which, we think, shows the error of computing diabetic statistics in this manner. The survey of the Civilian Defense was taken in all parts of Philadelphia and we believe it represents as good a sampling as can be obtained.

We were interested in the number of diabetic children attending schools in Philadelphia. Dr. Walter S.

Cornell, Chief Medical Examiner, made this survey for us. He states that there are only 140 known diabetic children attending the public, parochial and non-sectarian private schools, the combined total enrollment of which is 340,000. This is only .04%, but it is quite possible that many diabetic children, particularly those in the higher grades, conceal from their teachers and classmates the fact they have diabetes. It is also interesting to note that 250,000 physical examinations are done yearly by school physicians, but no urine analyses are included. To quote Dr. Cornell's report: "The average physical examination takes 7 minutes and costs the city 30 cents. Assuming that the same amount of time were consumed in doing urinalyses on 250,000 children, this would cost \$75,000 and would reveal the identity of 105 diabetic children at the cost of \$750 per revelation; and many of these children would already have been known to have diabetes". We may take issue with this estimate of the actual cost of running the urinalyses, but the fact remains that at present these are not included in the routine school examinations. Since diabetes in the young is an acute disease, seldom being present for a very long period before acute symptoms develop, we suppose that the number of cases picked up would definitely be small.

In conclusion, these surveys have been of great interest to us in Philadelphia, and we feel that while the study is not as accurate as we should wish or as many other studies have been, it nevertheless covers the largest group thus far analyzed; it at least indicates trends, and it presents a rather clear picture of what the causes of death among diabetics in Philadelphia are. It was surprising to learn that one-third of these people die of diabetic complications. We feel from limited surveys, not yet published, that patients in private and clinic practice do not fall into this group in anywhere near this high percentage. It is obvious that a broader educational program directed toward both physicians and patients would prevent many of these deaths and would result in increasing, by quite a few years, the average age of death in this group.

It has also been interesting to learn through the house-to-house canvass, that there are about 19,000 diabetics in Philadelphia. Our conclusions and figures are almost identical with those published by Dr. Lynch in his careful analysis of diabetic deaths in Boston in 1935, a study undertaken under Dr. Joslin's guidance. Our conclusions also coincide very definitely with the survey of 183 deaths in Cincinnati published in 1941. It is still obvious that far too many preventable deaths occur among diabetics and that wider publicity on its management is essential to decreased mortality.

Statistical Data from a Survey of Cases Reported on Death Certificates in Which Diabetes Was Listed as a Cause of Death in Philadelphia in 1940-1941-1942

Total number of "diabetic deaths" in Philadelphia	2499
Of these 53 were coroner's cases or were so indefinite as not to justify questionnaires	- 53
Total number of questionnaires sent out	2446

Total number of questionnaires received—718%	1768
Data considered insufficient	-189
TOTAL CASES ANALYZED.	1579
Average age at death of entire series	64.3
Average age at death in general in Philadelphia 1942	58.0
Cases in which diabetes was mentioned on certificate but in which the diabetes apparently contributed little to the actual cause of death	1029
Cases which died as a result of diabetic complications	550
TOTAL	1579

Number of Deaths

<i>Acidosis</i>	362
Average age at death	55.9
Deaths in patients less than 20 years of age	9
<i>Atherosclerosis</i>	376
<i>Coronary Artery Disease</i>	240
<i>Myocardial Degeneration</i>	91
<i>Miscellaneous</i>	
Carcinoma	95
Tuberculosis	33
Uremia	36
Leukemia	4

Civilian Defense Survey

Individuals Tabulated—34,633	Diabetics Reported—357
<i>Southeast Philadelphia</i>	
Zone 3	2,611 persons tabulated— 17 diabetics
" 5	1,202 " " — 3 "
" 9	84 " " — 0 "
<i>North Central Philadelphia</i>	
Zone 17	277 persons tabulated— 3 diabetics
" 18	20,375 " " —266 "
<i>Southwest Philadelphia</i>	
Zone 33	4,186 persons tabulated— 46 diabetics
<i>Mount Airy</i>	
Zone 42	538 persons tabulated— 3 diabetics
<i>Oak Lane</i>	
Zone 45	1,228 persons tabulated— 8 diabetics
" 46	4,132 " " — 11 "
TOTALS	34,633 persons tabulated—357 diabetics

Dr. Anderson:

I am going to call on another well-known figure in the field of diabetes to open discussion on Doctor Bendwood's paper: The Honorary President of the American Diabetes Association, Dr. Elliott P. Joslin of Boston.

Dr. Joslin:

I am very glad to open the discussion because I know it will be taken up and carried on by others—especially Mr. Marks of the Metropolitan Life Insurance Company, who may have more factual data. The one point that strikes me is the fact that more diabetes was found than had generally been expected and this should impress each one of us. This fits in with some work done by Blotner, Hyde and Kingsley who studied diabetes among army selectees. They also found very much more diabetes than had been anticipated. These new cases of diabetes are disclosed by hard work and detailed analyses. It means that a great group of people with diabetes is being discovered at an early stage and subjected to treatment much earlier than before, and consequently with much better results. I have also been impressed that in the Army soldiers have re-

sponded to treatment well. The good results are due presumably to early diagnosis.

I should like you all to know how much we all appreciate coming to New York for the New York Diabetes Association. I think the New York Diabetes Association is too modest—they should take advantage of the new aspects that are coming up in diabetes and use these as a means for collecting funds. They could with slight effort collect more than they have dreamed of.

There is much more diabetes than we have ever thought—how much more we can't say but there should be a great many more people interested in this disease.

Prior to 1914 the average diabetic, even in a private group, lived only 4.8 years—according to Dr. Beardwood's figures diabetics are living much longer and therefore should be deeply concerned about the disease, because of their own increasing exposure to complications.

The whole world is just on the edge of a new discovery in relation to the disease. This discovery was made by Dunn and associates of Glasgow through his series of experiments when studying the effect of various drugs on the body. Dunn found that alloxan destroys the Islands of Langerhans. Subsequently Bailey and Bailey of Boston found that on administration of alloxan to rabbits, they developed diabetes. This has opened up a marvelous opportunity for research.

The problem of heredity is another reason for success in securing funds. It is one of many which may be solved as a result of alloxan. My first private case of diabetes was in a patient I saw in 1897 just before I went to Europe. She died in 1899, 45 years ago, and now I am taking care of her diabetic grandniece and grandnephew, brother and sister. The increasing duration of life of diabetics exposes them to additional complications. I think the New York Diabetes Association ought to appeal to everybody for a contribution for its work. Even if each diabetic individual in New York City were to give only a dollar—think of the amount you would have for your educational activities, for the improvement of clinics, for children's camp, and for research.

Dr. Anderson:

Discussion of Doctor Beardwood's paper will be continued by Mr. Herbert H. Marks of the Metropolitan Life Insurance Company.

Mr. Marks:

The relatively high incidence of diabetes in the population surveyed by Dr. Beardwood and his group in Philadelphia raises the important question as to the adequacy of our present estimates of the incidence of diabetes in the country as a whole. Only recently there was published an excellent study of the incidence of diabetes among selectees at the Boston Induction Station by Dr. Harry Blotner and Major Robert W. Hyde with the assistance of Sergeant Lowell V. Kingsley (New England Journal of Medicine, December 9, 1943, page 885). This paper was based upon 45,650 consecutive selectees between ages 18 and 45 who appeared for final examination at the Station prior to induction in the armed forces. All the men had thorough physical and mental examinations, routine chest roentgenograms, and urine examinations. The test for sugar in the urine was with Benedict's qualitative solution and amounts of glycosuria were classified as 1+ to 4+ on the basis of the color changes. When sugar was found, the urine

was tested again before and after lunch on the same day, and if again positive and if there was not a verified history of diabetes, the men were sent to an Army hospital for sugar tolerance tests. The standard dose of 100 gm. of dextrose was used and was ingested after the subject had fasted overnight. Blood and urine specimens were taken during fasting and then ½, 1, 2, and 3 hours after the ingestion of the dextrose. Blood sugar determinations were made on venous blood by the Folin-Wu method. The authors also obtained information on the age of each man, his height and weight, residence, occupation, racial origin, and a number of other characteristics; for comparison they obtained the same details for a control group of non-diabetic men examined at the Induction Station.

Glycosuria of varying degree was found in 367 or 0.8 percent of the men examined. Presumably, this figure excludes those in which only the very first test was positive. The 367 cases were found to be further classifiable into three groups as follows: 208 cases of diabetes mellitus, 126 cases of transient glycosuria, and 33 cases of renal glycosuria. The criteria for the diagnosis of diabetes—and this has an important bearing on the results—were: blood sugar of 180 mg. per 100 cc. or more and glycosuria in one or more of the specimens taken after the ingestion of glucose.

On the basis of the 208 cases diagnosed as diabetes, the incidence of the disease was 4.6 per 1,000 registrants. At ages 18 to 25 this ratio was 2.0 per 1,000 and rose rapidly with age to 10.6 per 1,000 at ages 41 to 45. Of the 208 cases of diabetes mellitus, 107 were mild, 58 were moderate, and 43 were severe.

The results of this valuable study cannot be disregarded in any estimates of the prevalence of diabetes among young men in the United States. However, I do not think they can be accepted without reservation but require analysis and confirmation. The figures are much higher than those reported hitherto among American men in the same age span. They are, for example, 3 to 5 times as high as those reported at ages 20 to 45 in the National Health Survey (1935-1936). This is shown in the following table:

Massachusetts Selectees		(Males)	
Age Group	Number of Diabetics per 1,000 Registrants	Age Group	Number of Diabetics per 1,000
18-25	2.0	15-24	0.6
26-30	3.5	25-34	0.9
31-35	6.2	35-44	2.0
36-40	6.1		
41-45	10.6		

In part, the differences shown may be explained on the basis that some known cases escape enumeration in population surveys, as well as the undiagnosed cases. In addition, there has been a steady and sizable increase in the incidence of diabetes at the younger ages in the interval since the National Health Survey because more young diabetics have survived while the incidence of new cases may be presumed to be stable. The combined weight of these factors, however, is not sufficient to make up the entire difference, and there are several reasons why one should hesitate to assume that the Massachusetts figures are representative. From the statistical point of view, the chief considerations are these: 1) The actual number of diabetics reported is not large—208 altogether. 2) The experience is largely urban. Previous studies have shown that the prevalence of diabetes in such areas is higher than in the country. 3) Exceptionally high ratios were found among the Jews and Irish who form a much higher proportion of the Massachusetts' population than of the population of the country as a whole. Among the men of native American stock, the ratio of diabetics was 3.5 per 1,000 as compared with 4.6 in the entire experience. 4) The previously known diabetics numbered 42, or 1 per 1,000. This ratio is practically identical with the ratio for men between 20 and 45 in the National Health Survey. 5) The Massachusetts figures for diabetes appear high in relation to the frequency of glycosuria among unselected men of the same age. There are numerous reports

on the latter, based on industrial, student, life insurance and periodic health examinations, and only a fraction of these glycosurics were diabetic. 6) The proportion of overweights is surprisingly low.

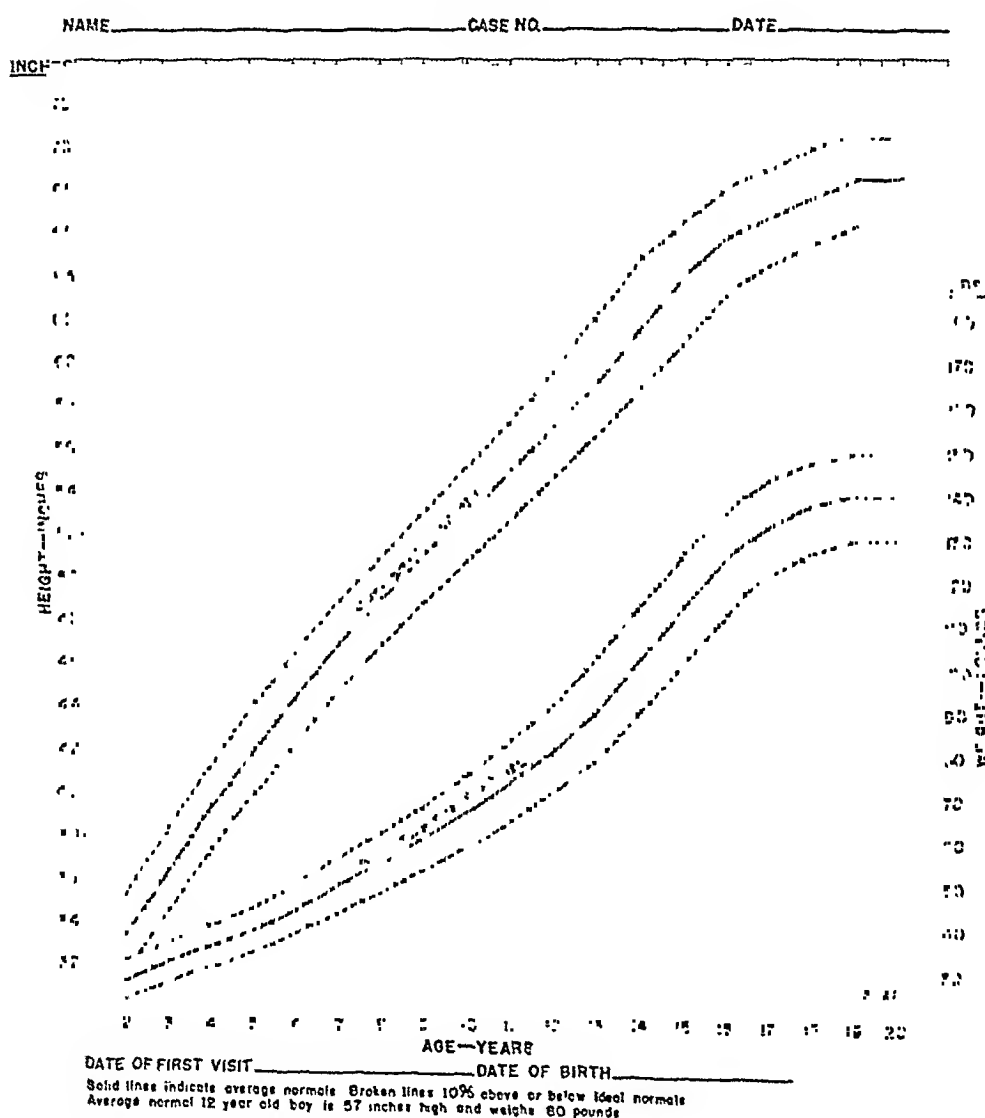
Apart from these statistical considerations, the incidence of diabetes in this Massachusetts study, largely based as it is on laboratory findings only, seems high on other grounds. The circumstances attending examinations for induction to military service are by no means ideal. Notable, for example, is the degree of nervous tension which undoubtedly gives rise to numerous cases of transient glycosuria just as has been ob-

even by laboratory standards, comparatively mild. The low incidence of obesity has already been mentioned.

All this suggests that further study of the cases not previously known to be diabetic would be well worthwhile, as well as similar studies in other centers. It is, of course, proper that these men be disqualified or at least postponed for military service, but it might be advisable to defer the final diagnosis in many instances.

Although I have raised these many questions regarding the study of Blotner and his associates, they are criticisms of detail rather than of the essential worth of the study. It is an

CHART I
GROWTH CHART—MALE



served, for example, among college students during scholastic examinations and in athletes immediately after a game. Among the latter, hyperglycemia as well as glycosuria has been noted. I would call attention also to the limitations of the glucose tolerance test. It is an abnormal procedure and it is influenced by a number of factors, such as previous diet, infections, and endocrine disorders. It is not infrequent in clinical and life insurance experience to get different results on successive glucose tolerance tests on the same individual. The high proportion of cases without a previous history of the disease is surprising in view of the clinical experience regarding the nature of the onset of diabetes at these ages. In this connection, it is notable that most of the cases were symptomless, and

excellent piece of work and gives good evidence that our estimates of the incidence of diabetes may have to be revised upwards to an appreciable extent. How great an adjustment is to be made would be indicated by intensive follow-up study in border-line cases, as well as further extensive studies of the incidence and type of glycosuria in men examined for the armed services.

Dr. Anderson:

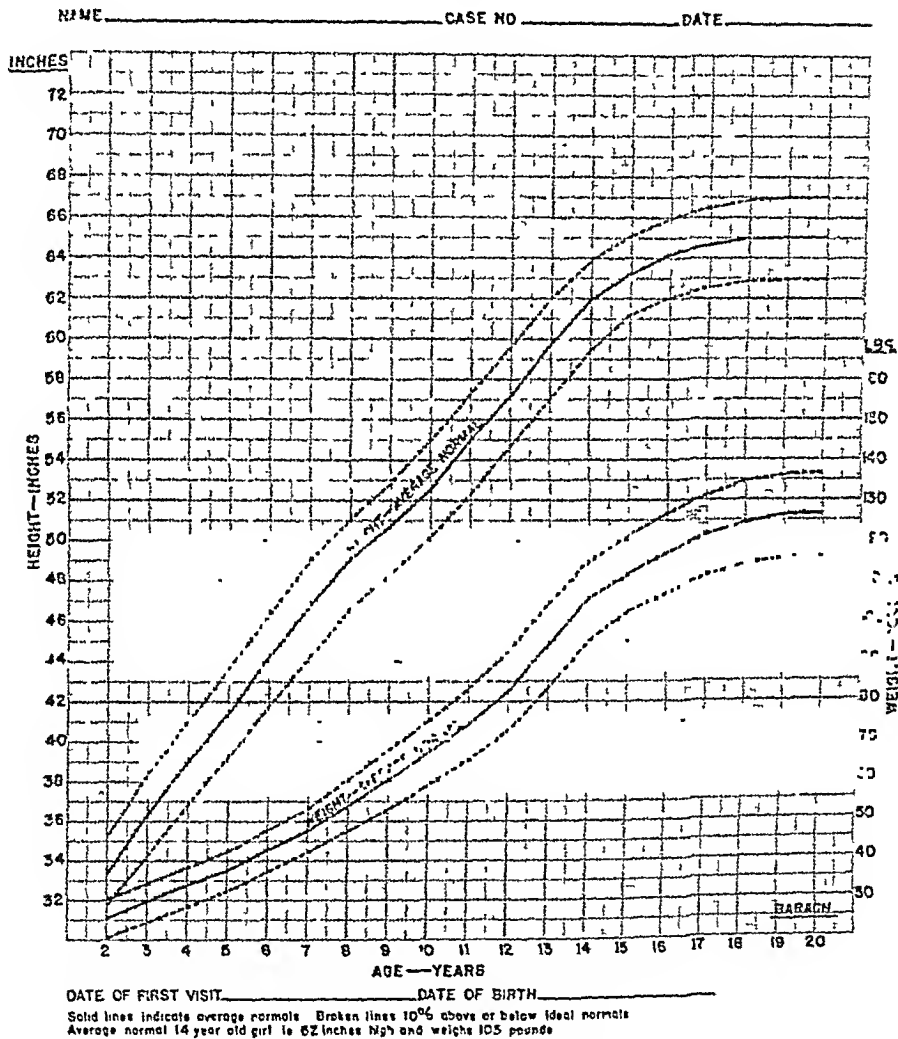
The second paper of the evening will be on the subject of "Normal Standards in the Treatment of Young Diabetics" by an outstanding authority in this field, Dr. Joseph H. Barach of Pittsburgh.

"Normal Standards in the Treatment of Young Diabetics", Joseph H. Barach, M.D.

A man working with adult diabetics throughout the day may find himself in a state of mental comfort until unexpectedly a juvenile diabetic is brought before him. He will do well enough while taking the history of the patient, while doing the physical examination, and even in prescribing the diet to render the patient sugar nor-

state for a child of this age?" He may then bring out his favorite table for comparison with the so-called normals. If, perchance, he is not altogether satisfied with the results of this comparison and he brings out another set of tables (for there are many different ones), he may find that the second one is lower or higher in values than the first. If this is disturbing, he may look up one more table and find high values

CHART II
GROWTH CHART—FEMALE



mal; but that is far from covering the entire problem. At this point he finds himself facing a very realistic project. He must try to maintain a sugar normal state for a very sensitive patient; he must plan to meet the metabolic requirements from day to day, and above all, he must draw a blueprint for the nutritional needs of a growing child and youth in years to come. In this planning for the future, he will need to evaluate the patient's nutritional state as of today. He must then ask himself, "Is this child of normal growth for his years or is he in a state of undergrowth or overgrowth? If not normal, what is the normal or optimal

that are higher than his heretofore highest values and low values that are lower. All of this is disconcerting, and he may quit, murmuring to himself "A plague on all your houses." On the other hand, he may decide to see it through all the way and continue from one authority to another, as I did, until I had reviewed fourteen of them. After that, I found myself in the hands of the Anthropologist, Anthropometrist, and the Mathematician, who proceeded to solve the problem with mathematical equations, the full implications of which I did not understand. I am quite sure also that he did not understand the medical im-

plications of the equations. Because of all this, I have decided that it will be better if I change the title of my paper from "Normal Standards in the Treatment of Young Diabetics" to "A Search for Normal Standards in the Treatment of Young Diabetics".

For the purpose of this study I analyzed fourteen of our well-known tables, the first four of which were based on measurements of 211,827 children of average normal health, at various ages, and out of these constructed the following charts for the male and female. (Charts I and II attached.) So far as I can see, these values give us a true starting point for what is normal, and if we allow a ten per cent variation above and below the midline, we are well within the normal zone. By plotting the patient's age, height and weight records on the normal curves we can see immediately whether our patient is taller or shorter, lighter or heavier than normal. Our chart reveals the time at which growth is retarded or accelerated, the rate of growth and the ultimate growth attained.

Calories: If, by the use of these charts we have come to know what is the desired height or weight of a patient at a given age, then we may proceed to the next step. How many calories per day shall we give to our patient? Should one believe that this is a simple question, one need only to review the various authorities on nutrition. Here again one will find that authorities differ. One will find that for a child of twelve, diets are being recommended which vary from 1,200 to 3,600 calories per day. It would seem that both cannot be right; nevertheless, one will find such authorities as Medical Research Council of England, New Health Society Report, London, National Research Council, U.S.A., League of Nations Bulletin, DuBois, Priscilla White, and others, each following standards quite different from the others.

Protein: Then comes the question of protein allowance for the growing child. Here one finds the National Research Council, U.S.A., the League of Nations Committee on Nutrition, various individual workers in France and in this country, recommending widely varying amounts of protein; some of them at certain ages are twice as great as others. One wonders if such widely differing values can be equally physiological or optimal, in health and in disease.

If one reviews the experimental studies of various authorities on adult nutrition one finds that experiments over long periods of time reveal that an adult will maintain equally good health and performance on protein rations varying from 50 to 160 grams per day. One finds experimental proof in men living under controlled conditions on 25 grams of protein per day with vigorous daily exercise, even to climbing of mountains 14,000 feet above sea-level. There is good evidence that protein is as well metabolized in warm as in cold climates, and that a daily ration of 50, 100, or 150 grams of protein is compatible with normal good health.

At this point I wish to say that while all of this may be true for a man in full normal health, it need not be all true for the diabetic. We know that the liver of the diabetic is not normal and cannot function

normally. We know that a high protein diet requires a fully adequate water exchange, and that the capacity of the diabetic in that respect is not normal. We know that a high protein diet may be followed by azotemia, and azotemia is present in ketosis and diabetic coma; anything conducive to accumulation of nitrogen products in the blood is bound to be harmful. We know that the liver is the site for most of the pathologic physiology in diabetes and we, therefore, infer that it is unwise to over-load that liver in any way. Because of these factors, we allow our diabetic patients a moderate protein ration, one that is at the lower physiological levels. Such portions when calculated, amount to about 15% of the total daily caloric allowance.

Fat: One avoids excessive fat in the diet after allowing an adequate amount of milk sufficient to meet the normal requirements of growing youth and its needs for minerals and vitamins. Ever since 1924, we have been devotees of the higher carbohydrate diet. With these concepts in mind we have constructed a table of diets to meet the above conditions.

Adequate Diets: The diets in our plan obtain 50% of their calories from carbohydrate, 15% from protein and 35% from fat. Were it not for the desirability of giving rather large amounts of milk, we could get

TABLE OF DIETS
Maintenance Diet For Growing Children (50% of
Calories from Carbohydrate, 15% from Pro-
tein, 35% from Fat)

AGE	WEIGHT		MAXIMUM DIET NORMALS Daily Allowance				MINIMUM DIET DIABETES Daily Allowance			
			Calor- ies	Carbo- Hy- drate Grams	Pro- tein Grams	Fat Grams	Calor- ies	Carbo- Hy- drate Grams	Pro- tein Grams	Fat Grams
Years	Lbs.	Kilos								
1/2	15	7	700	90	30	25	600	75	25	25
1	20	9	1000	125	40	35	800	100	30	30
2	26	10	1100	140	45	40	880	110	35	35
3	31	14	1200	150	50	45	960	120	40	40
4	35	16	1300	165	50	50	1040	130	40	40
5	38	17	1400	175	55	55	1120	140	45	45
6	43	19	1500	185	55	60	1200	150	45	50
7	50	22	1600	200	65	60	1280	160	50	50
8	55	25	1700	215	65	65	1360	170	55	55
9	61	28	1800	225	70	70	1440	180	55	55
10	67	30	1900	235	70	75	1520	190	55	60
11	75	34	2000	250	70	80	1600	200	65	65
12	81	37	2100	265	80	80	1680	210	65	65
13	90	40	2200	275	85	85	1760	220	70	70
14	103	47	2300	285	85	90	1840	230	70	70
15	112	50	2400	300	90	95	1920	240	75	75
16	126	57	2500	315	95	95	2000	240	80	80
17	133	60	2600	325	100	100	2080	240	80	90
18	138	63	2700	340	100	105	2160	240	85	95
19	138	63	2800	350	100	110	2240	240	90	100
20	139	63	2900	365	100	115	2320	240	95	110

1. After age 16, girls weigh 10% less than boys.
2. Caloric values of Diabetic diets are 20% below full normal diets; this may be increased to full normal when desirable.
3. After age 15 when growth rate slows, Carbohydrate portions remain same, Fat may be increased. A lower fat diet may be attained by substituting 2 grams carbohydrate for one gram fat in the daily diet.
4. These diets obtain more calories from Carbohydrate and Protein than from Fats.
5. In these tables fractions have been disregarded in favor of round numbers.

along with less fat and larger portions of carbohydrate; but milk is an ideal food for the growing period of life; it is physiological and it is palatable, and therefore it is highly desirable. (See "Table of Diets".)

150 Diabetic Children: On the basis of our growth charts and what we call adequate diets, we have recently analyzed the nutritional status of 150 young diabetics. Among these we find that 25 were of normal height and weight for their years. On our chart we find their plotted lines, so to speak, right on the beam. Fifty-seven were under-size in height and weight, and 53 were over-size. On calculating the values of the diets on which the normal-sized children were subsisting, we found that 9 had attained normal growth on a diet actually below our minimum adequate diet and 16 had a fully adequate diet. Of the 57 who were under-size, 30 had been subsisting on a diet that was actually below what we now consider adequate and the other 27 were on a maintenance diet. Of the 53 who, according to our present standards, were over-size, 31 had more than a full normal diet and 22 had even more than that, *luxus* diets. Thus it becomes evident that where the diet was inadequate we find retarded growth, where the diet was excessive we find overgrowth, and according to our evaluations, both of these are avoidable in 80% of the cases. Our studies also reveal that the over-growth group with their *luxus* diets required an average of 55 units of insulin daily, whereas the group on more normal diets required only 32 units per day.

Thus, we conclude that we can control the growth of the diabetic child to a very large extent by supplying a normal diet, by carefully avoiding inadequacies and excesses. We can accomplish this if we have a plan and follow that plan. It is our custom to glance at the growth chart at every visit of the diabetic child and to see "whither we are going".

Atypical Cases: There are, of course, cases which do not respond normally to adequate diets. Our experience indicates that faulty sugar control in diabetic children does not retard growth. Too many of our children who disobey their diet restriction grow normally and well. Not only did our "bad boy" grow well and strong, but our very best boy, our perfect patient, remains a diabetic dwarf. There are those who seem to attain full normal stature on diets which are definitely below our conception of normal values, and there are those who have failed to grow regardless of high caloric diets, high protein, and high fat portions, additional vitamins and growth hormones; nothing that we gave them has altered their immovable growth pattern. Along with these we have met with patients who had congenitally small pancreas, almost without the Islands of Langerhans and with almost no tissue for the manufacture of external secretions of the pancreas, and these remained dwarfed.

The one thing which these studies brings out clearly is the absolute need for planned treatment in the care of the young diabetic. Anyone who would do less than that should not accept the responsibility of treating the young diabetic patient. On the other hand, if one does follow a plan which constantly aims at the normal, he

will be sure of his procedure and he will be rewarded by good results.

Dr. Anderson:

Doctor Barach's paper will be submitted to the round-table panel on diabetes for discussion. I wish to take this opportunity to introduce the other participants on the evening program: Dr. J. West Mitchell of Pittsburgh; Dr. Cecil Striker of Cincinnati; Dr. Seale Harris of Birmingham, Alabama; Dr. Howard F. Root of Boston; Dr. Edward S. Dillon of Philadelphia.

Before embarking on the discussion it gives me great pleasure to introduce to you a life-long friend of the late Major Sir Frederick G. Banting, Dr. Frederick Hipwell of Toronto, who has graced this meeting by his presence.

Doctor Mitchell, will you kindly open the discussion?

Dr. Mitchell:

First I should like to express my appreciation of the invitation to come here to the meeting of the New York Diabetes Association. It is indeed a great honor. To attempt satisfactorily to discuss this paper of a colleague with whom I have worked for the last fifteen years, is very difficult. I know that in the preparation of this paper and charts, Dr. Barach almost caused a number of psychoses on the staff. I hope that the audience will ask a great many questions as these graphs represent a prediction chart of what we may expect these children to do under guidance. We haven't tried these curves long enough to know if they will tell us about the development of the diabetic dwarf. We haven't followed them long enough to know if we can back up any of the individual causes for altered height and weight. They are so logical that we may hope that we have here the way to predict the course of development in these children, a very important thing to be able to do. We hope somebody will ask questions about essential amino acids, fatty acids, the influence of vitamins on growth, and so on, because these are problems which we must solve in our every-day therapy of the diabetic child who is most of the time a very nice person but a little hard therapeutically to get along with.

Dr. Striker:

I should like to continue the discussion in view of the fact that one of the questions given to me was: "To what extent do you permit glycosuria in juvenile diabetics?"

I think that this problem should be discussed from two angles: 1) What are our criteria for the general welfare of the child? and 2) What do we understand by dietary control?

In the first instance when one sees these diabetic children over a period of fifteen or twenty years and sees them grow, have normal bone development, and, in spite of this, have persistent glycosuria, one must define what he means by normal criteria. I assume that the main criterion is normal development, irrespective of absence or presence of glycosuria. I think the tendency should be to minimize glycosuria. I do not mean that we should not make examinations of the urine and blood, but I should like to ask, other things being equal, where there is no dehydration, no acetoneuria, and no deficiency in bone development, and where we have good body development, what else do we need?

This opinion is fortified by the all too many unfortunate experiences we have had when we try to keep these children completely aglycosuric. When one repeatedly sees insulin reactions and when one has frequently to resort to glucose intravenously, I think that one at least should be open to the suggestion that aglycosuria is either ill-advised or impossible.

In the second instance in regard to the question of dietary control, I wish to say that as a member of a sub-committee of the National Research Council which considered diabetes in regard to food-rationing, I attempted to set up a "dietary

yardstick" for diabetes in order to establish their right for extra food rations. In a rather detailed survey from men who are interested in diabetes, we got some very wide ranges of what was considered a proper diet for the diabetic. These figures range from one hundred to three hundred grams of carbohydrates, from sixty to one hundred and ten grams of protein, and from thirty to one hundred and seventy-five grams of fat. Under these circumstances, I ask myself and you, what type of definition will cover adequate control of diabetes? In view of the wide variation in the diets used, it seems illogical to interpret our results only on urine-sugar and blood-sugar determinations. The question is still wide open and I feel that we should have at this time only a fluid concept of the standards to be used.

Dr. Root:

We recently had at the Deaconess Hospital a young man, aged 36 years, who arrived feeling that his usefulness in life was about to terminate. He had had extremely severe pain in his legs and in other parts of his body—neuritis of such a character that he was confined most of the time to bed. He finally learned that it made a difference whether with a diet of 150 grams of carbohydrate he passed 150 grams in his urine. He had been treated in an excellent diabetes clinic, but over a period of five years of careful observation, he had not learned that it made any difference in his nutrition whether the urine contained 150 or 15 grams of glucose.

No sane diabetes specialist really thinks that the control of the diabetic depends solely on the presence or absence of glycosuria. Dr. Tolstoi certainly knows this perfectly well. We all know that it makes a big difference whether the diabetic patient excretes 50 or 100 percent of his carbohydrate intake. The control of diabetes means the maintenance of such a balance between the proper diet and insulin received by injection (as well as that secreted by his own pancreas) so that the good is gotten out of the diet consumed and the person is properly nourished. When these conditions are met, the blood sugar varies within a normal range.

With regard to the pancreas: some time ago I analyzed the weight of the pancreas in relation to the weights of other organs of the body. As you all know, when patients have an over-active pituitary and develop acromegaly, there is an increase in size of all of the organs of the body and also of the pancreas. In Simmond's disease, on the other hand, the pancreas is undersized. If the patient has a small pancreas and a small liver and heart, then it is a fair general assumption that there has been a hypo-active pituitary.

Dr. Lukens of Philadelphia was interested in this problem and analyzed the data. We are now working on a large series, and there is rather good evidence that some connection exists between the pituitary gland and an extraordinarily small pancreas. It may be an inherited deficiency that prevents the normal growth of the pancreas. We all have seen cases where an extraordinarily small pancreas is present and where usually there have been rather peculiar features about the growth in childhood or about the diabetes in adult life.

Dr. Anderson:

I note the presence of Dr. Edward Tolstoi in the audience. Since his name has been mentioned, I shall yield to the temptation to call him to the platform.

Dr. Tolstoi:

I am very happy to learn that Dr. Root does not pay too much attention to glycosuria when using protamine insulin. This is very gratifying, as it represents a change of viewpoint, for I know that over many years he was insistent on sugar-free urine. If we concur on this particular point, we really aren't very far apart. Now as to criteria for good control, mine have been: normal growth and development, normal physical and mental activity, and ability to "carry on". If a patient can attain all of these, even though he excretes some sugar, I don't worry too much about the glycosuria so long as he has no symptoms of diabetes, such as thirst, hunger, polyuria, etc. He may excrete 40 to 50 grams of glucose in 1,500 cc. of urine during a twenty-four hour period and carry

on a perfectly useful life. That he may get along well for a period of years we have observed since the introduction of protamine insulin. I have some patients who do just that. When you see many patients of this type, you cannot help but be impressed.

I was particularly attracted to Dr. Barach's chart of the "bad boy" who, in spite of a continuous glycosuria for nearly six years with occasional ketosis, grew and developed in normal fashion.

Dr. Joslin's teachings have been the "bible of diabetes" for most of us. However, with the introduction of new techniques, new facts reveal themselves. These at times necessitate the revision of a viewpoint, and when certain truths are established, one cannot help but accept them. As a scientist I am bound to accept the facts as I find them.

Dr. Anderson:

Doctor Tolstoi's views have been the subject of polemics before New York audiences in the past. I shall entertain at this time one of you gentlemen who would moderate in this question or champion a mid-way course.

Dr. Dillon:

Mr. Chairman, I had not expected you to call on me as a dissenter. But as a matter of fact, I do disagree very strongly with some things which have just been said.

In regard to whether or not it is good therapy to have sugar in the urine of patients whom we are treating for diabetes, let me make it clear at once that I am not talking about insulin-sensitive patients. The blood sugar level of these patients often makes very large and rapid changes, up and down, or down and up, in only a few hours, and it is, in these patients, impossible to keep the blood sugar level at all times above the hypoglycemic shock level or below the renal threshold. We have to be satisfied to keep the whole twenty-four hour blood sugar pattern at a higher level in order to avoid dips into shock levels. As has already been pointed out this evening, frequent severe shocks are harmful, most unpleasant for the patient, his family, and his attending physician, and must be avoided. But in these insulin-sensitive patients, it is impossible to avoid shocks and at the same time prevent the blood sugar level from making excursions above the renal threshold, which, of course, results in glycosuria. The amount of sugar in the twenty-four hour specimen may be quite large. I prefer to regard this glycosuria as something which we cannot avoid—the lesser of two evils. I do not like to regard this glycosuria as something which is desirable or as a badge of good treatment, for the reason that doctors and patients alike soon come to regard glycosuria as something which is desirable for all diabetics.

For anyone who is treating large numbers of diabetics, these insulin-sensitive patients constitute a considerable proportion of his patients. They are difficult to control and tend to gravitate to the specialist. However, they do not constitute a large proportion of the total number of diabetics encountered. For the physician who understands the principles of diet and who is familiar with the actions of regular insulin and protamine zinc insulin, it is usually not a difficult task to keep the urine of the vast majority of diabetics free from sugar and at the same time avoid hypoglycemic shock.

I am well aware that there are careful and reliable physicians who pay little attention to the presence or absence of glycosuria and whose patients seem to be maintained in good condition over long periods of time. You will note, however, that these doctors always state that the glycosuria is harmless "if" the patient has no polyuria, polydipsia, or polyphagia, "if" his weight and strength remain good, "if" he has no ketonuria, "if" the amount of sugar in the urine does not exceed a certain quantity per twenty-four hours, etc. With regard to the last criterion, the patient's Benedict tests done at home by these patients are likely to be red whether the twenty-four hour specimen contains twenty grams of glucose or one hundred and twenty grams, and so home tests stand of little value. If for all of the above "ifs" this "if" is sub-

thinned, i.e., "if the urine is kept sugar-free", all of the above "life" automatically disappears.

Persistent glycosuria usually means a certain degree of persistent hyperglycemia. Does persistent hyperglycemia do any damage to the I-islets? I believe that it at least prevents recovery of lost function and may result in further loss of function. Does persistent hyperglycemia do any damage to the arteries of the legs, to the coronary, and to the retina; or are some other concomitant metabolic products responsible for the damage? The whole story is not known. However, insofar as I can be sure of anything from clinical experience alone, I am sure of this—that those diabetics who have legs because of arterial disease, those who develop coronary atherosclerosis at a relatively early age, and those who develop retinitis, usually have had diabetes which has been mild, but out of control, and over a long period of years.

I, therefore, think that it is bad doctrine to preach to the general practitioner, who must necessarily see the bulk of the diabetics, that glycosuria is harmless, because for the general practitioner the presence or absence of sugar will continue to be the most available and most easily understood measuring rod of the control of diabetes. If he permits his patient to have twenty prisms in the urine with complacency, he is unlikely to be on the alert for one hundred and twenty prisms, or for any of the above important "bits".

When and if the day comes that blood sugar determinations are more generally available and the manner in which the blood sugar level fluctuates with reference to meals is more widely understood, the kind and amounts of insulin the patient is taking, etc., then we may be better able to advise that glycosuria may not be so very important.

Dr. Johnson:

Doctor Harris, would you please discuss the criteria of hyperglycemia, including hyperinsulinism and paroxysmal hypoglycemia, and perhaps discuss alloxan?

Dr. Harris:

I appreciate the privilege of discussing hyperglycemia and admit that I don't know anything about it—which is probably why I am willing to discuss it. Hypoglycemia, also called hyperinsulinism, is, of course, the same thing that is induced by an over-dose of insulin. Every symptom that has been reported from an over-dose of insulin is the same for spontaneous hypoglycemia. One criterion is finding the blood sugar below normal. There are many patients with hypoglycemia who have no symptoms whatsoever. Hyperinsulinism or spontaneous hypoglycemia make a much more frequent appearance than does diabetes. If you will study case histories of diabetes, a very considerable number of them will give histories of hypoglycemic attacks years before they develop diabetes. One of the causes of obesity is hyperinsulinism or spontaneous hypoglycemia. They have the appetite for food—they have to eat in order to be comfortable. Overwork the pancreas, and there may be a change from hyper- to hypo-insulinism. Joslin and Wilder have said that if diabetes had been discovered only today, inasmuch as it is really "hypo-insulinism", this is what it might have been called rather than "diabetes". It is a deficiency disease, a deficiency of insulin.

Lee Warden at Johns Hopkins reported 425 cases recorded as hyperinsulinism and about twenty-five percent of them had no symptoms whatsoever. Some had no more than one would get with an over-dose of insulin. On giving an over-dose of insulin or when spontaneous hypoglycemia occurs, some patients will become delirious and psychotic—some will have convulsions; others even with very low blood sugar may have no symptoms whatsoever. The question is entirely a relative one. With regard to criteria, the diagnosis depends to some extent on the type of disturbance and the pathology as well as its severity. Consider the adenoma of the islet cell. The best piece of work in this respect is by Whipple of New York City. I have found that some cases of epilepsy are erroneously diagnosed and are really cases of spontaneous hypoglycemia. I have studied certain cases of epilepsy. I have operated on patients suspected of having adenoma, patients with a blood sugar of below 40 mgms. percent. One should also consider as

related to the problem certain pituitary disorders. There are waves of pituitary secretion as Cushing pointed out.

As to blood sugar curves—a three-hour blood sugar study for hypoglycemia is not of a great deal of value and is often misleading. Carry your blood sugar studies over six or more hours. Hypoglycemia usually occurs in five hours or more after the meal. A very considerable number of patients I have seen did not have hypoglycemia on a three-hour curve but developed it only on a five- or six-hour curve. A six-hour glucose tolerance test is necessary if one is to make an accurate diagnosis of hyperinsulinism.

There was a patient in Savannah—they studied her at Duke University and had made six glucose tests. They had found her to be practically normal and yet she continued to have coma attacks at night. She proved to have an adenoma of the pancreas. One must not depend on one or two or three blood sugar curves. One has to consider the question of symptoms of the patient. One makes a correct diagnosis only after careful study of the patient.

With regard to the question of alloxan: I am frank to say that I know very little about it. Joslin has already pointed out that with it you get destruction of the I-islet cells of the pancreas. This is an observation which has a great deal of importance. It may be that if the proper dosage could be found, one could safely reduce the secretion of the I-islets. I don't believe we should go into such therapeutic experimentation unless we are prepared to make very thorough studies beforehand. I think that alloxan is capable of a great deal of harm unless handled with extreme care.

Dr. Anderson:

Doctor Root, will you please discuss the use of glucose by vein in the treatment of diabetic coma?

Dr. Root:

This problem is not simple nor is it uncommon. The premature use of glucose in diabetic coma is a practice which is cutting off many lives right now. I am grateful to Dr. Beardwood who has shown that diabetic coma and acidosis are still a major cause of diabetic death. We hear the remark occasionally made: "I haven't seen a diabetic death from coma in years." Such a remark is usually made by a person who hasn't searched the records of his hospital. Actually in the last few months we have been accumulating a few cases in which doctors have asked the question: "Why did this patient die? I gave him glucose on admission when he had coma and yet he died."

There are three "lacks" in diabetic coma: 1) a lack of insulin; 2) a lack of carbohydrate oxidation (Since the patient in diabetic coma derives his calories from fat, one gets excessive ketone body formation.); and 3) a lack of water and salt.

Lack of insulin is the most important. Therefore, adequate insulin dosage is the primary problem. What insulin dosage is needed is the first question. The diagnosis of diabetic coma means that a genuine emergency exists and unless proper insulin treatment is begun immediately, the patient may rapidly progress in a few hours into a state where irreversible changes have occurred. Two important facts about insulin are forgotten in treating coma. First is that there is marked insulin resistance so that a dose of 100 units may give only the effect which you expect to see with 25 units in a person not in coma. Second, the law of diminishing returns applies to insulin; that is, with the first 100 units you may only get 50 units of anticipated effect, and so on. If the patient really needs 500 units and does not get it for ten or twelve hours, an opportunity is lost.

Worst of all, doctors fail to realize that glucose neutralizes the action of insulin. If a patient has a low blood sugar due to an over-dose of insulin or if he has a hypoglycemic shock due to treatment of schizophrenia with insulin, the one effective remedy to counteract such effect of the insulin is the administration of glucose. When one gives glucose to a patient in diabetic coma, one prevents the action of insulin in lowering the sugar of the blood and one may thereby greatly increase the amount of insulin which the patient will ultimately need for recovery. The giving of glucose raises the blood sugar, in-

creases polyuria and dehydration. In two cases recently seen by me death resulted because insulin was given "too little and too late." In one, a child of fourteen years, Karo corn syrup was given by stomach tube and glucose solution was injected by vein to the amount of 250 grams. At the same time the doctor ordered only 30 units of insulin every two hours. The patient never became sugar-free. Diacetic acid never disappeared from the urine. The child died when he might easily have recovered if no glucose had been given at the outset of treatment and if a moderate dose of 100 to 150 units of insulin had been given immediately.

In the early mild case of ketosis, the harmful effects of glucose are concealed by the beneficial effects of insulin. The moderately severe case of coma may be transformed into a severe one by the use of glucose and the insulin requirement thereby greatly increased. In the far advanced case of coma, the administration of glucose solution will bring on the terminal anuria with resulting death.

Dr. Beardwood:

I am not on the panel, however, I should like to say a few words about the use of glucose in diabetic acidosis.

By implication, the slides presented by Dr. Root, seem to show that the patients were killed by the use of intravenous glucose. I feel that this is not Doctor Root's intention and certainly has not been our experience. It is obvious that glucose should not be given in too large doses and that adequate insulin should be given at the same time. It has been our custom to give a *small* dose of glucose after an adequate preliminary dose of insulin.

We have seen some patients who died as a result of excessive insulin dosage and insufficient carbohydrate. I must agree with Doctor Root that the early and excessive use of glucose is contra-indicated, but I cannot agree with him that judiciously used glucose with sodium lactate and other methods of therapy are not of great use in the treatment of diabetic acidosis.

Dr. Anderson:

It would seem that the use of glucose by vein in diabetic coma would depend much on the time element. In the early stages when insulin function is at a low level its use would appear to be futile and detrimental, if only because of promoting further harmful diuresis and electrolyte loss, whereas after insulin function has been established, its employment might easily forestall land-slide insulin effect and hypoglycemic shock.

Dr. Anderson:

Doctor Dillon, what is your attitude toward the treatment of diabetics who run high blood sugar with high renal threshold of hyperglycemia without glycosuria?

Dr. Dillon:

Normal individuals vary widely in regard to the height of the blood sugar level necessary for the appearance of glycosuria. Diabetics show this same variation, but in addition, diabetics tend as a whole to have higher renal thresholds than do non-diabetics. Renal thresholds in diabetics above 200 are rather common. These elevated renal thresholds usually occur in older patients, and arteriosclerosis, hypertension, or chronic nephritis, are often present also.

The question immediately arises as to whether we can safely disregard a moderate hyperglycemia if there is no glycosuria. Should a patient who is taking no insulin be advised to take insulin, or if he is already on insulin, should the amount of insulin be increased until the blood sugar is reduced to a lower level? If there is no sugar in the urine, it is highly improbable that the patient will have any immediate ill-effects from the high blood sugar. In fact, he is likely to be feeling fine. From the long-range point of view, as I mentioned earlier this evening, I think there are two very good reasons why we cannot entirely disregard the high blood sugar, in spite of aglycosuria. The first reason is that the patient's tolerance tends to grow worse. Just as heart patients in whom the myocardial reserve is poor must have rest, so in diabetes one of our cardinal principles of treatment should be to rest the Islets. Presumably the Islets are working to maximum capacity so

long as the blood sugar level is much above normal. Whether this is good theory or not, it is a matter of common experience that if the blood sugar level is allowed to remain persistently high, the amount of insulin required to prevent a still higher rise of blood sugar tends to increase. Likewise, after the blood sugar level has been reduced from a higher to a lower or more nearly normal level and maintained at the new level for a few days or weeks, then it is frequently necessary to reduce the daily maintenance amount of insulin to a new and lower amount, lest hypoglycemia will result. Presumably, under these circumstances, there has been some recovery of function of the Islets.

The second reason for paying attention to high blood sugar is that I fear arteriosclerosis. I do not know whether hyperglycemia without glycosuria tends to create the necessary conditions for the development of arteriosclerosis. I do know that I have seen a great many leg-amputations because of gangrene, and that nearly always these patients have given one of the following three histories: 1) they did not know they had diabetes until the onset of gangrene; 2) they had known for years that they had diabetes and had received good medical advice, but had not followed it; 3) they had been told years ago that they had sugar in the urine, but had not been advised that there was anything serious about that, and had simply been told not to eat "any sugar, pastry, bread, potatoes, etc."

Our standards of treatment should be high. We should aim to make our diabetic patients as nearly like normal people as we can, and we should not condone departures from normal—in this instance, hyperglycemia, unless in our efforts to correct one departure from normal, we create another less desirable one—hypoglycemia.

Dr. Anderson:

The lateness of the hour obliges us to leave many questions unanswered. On behalf of the New York Diabetes Association, I should like to thank our guest speakers for their contributions to this evening's program, the success of which is attested by the interest of this large audience. Before adjourning, may I ask one last question of Doctor Joslin? Is the old axiom true that diabetics resist infection and heal wounds poorly; if so, what is your explanation for this?

Dr. Joslin:

To this question, I can answer yes—the old axiom is true. A surgeon would say no. He would, however, be more cautious about the diabetic than the non-diabetic. Tuberculosis is more common in the diabetic than in non-diabetics. Skin lesions are more common with diabetes. In the early days it was said that every diabetic (this was, of course, long before insulin) with pneumonia would die. I remember how hard I tried to show that this statement was not true. On the other hand, Dr. Geyelin pointed out that the diabetes after an infection is not necessarily worse than before it.

The discovery of insulin brought this point out still more strongly. Infection makes diabetes worse. During the recently prevalent infection, influenza, I have been seeing patients who became much worse, but with an extra dose of insulin did well. We should remember in all this talk about infection in diabetes that now we treat diabetics with insulin and in treating them thus, the diabetic becomes an almost normal individual. I like to think of it this way. You take a severe uncontrolled diabetic and have him exercise violently and his blood sugar will go right up. Then have him under adequate insulin and give him exercise and he will respond like a mild diabetic or a normal individual. So it is with infection. Have your diabetics well controlled with insulin, for it is when they are caught unexpectedly they get into trouble. Why is the diabetic susceptible to infection? Is there less insulin? Are the pituitary and thyroid over-stimulated? Or is it due to lessened glycogen deposition in the liver? Dr. Mosenthal brought out the fact that during infections in uncontrolled diabetes dehydration and acidosis all complicate the situation. During an infection also the metabolism is raised and this is harmful. In infections in the lower extremities arteriosclerosis is important in the diabetic. The picture, therefore, is quite a complicated one.

Observations on the Possible Pathogenicity of Paracolon Bacilli as Incitants of Diarrheal Diseases in Infants and Children

By

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and

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THE paracolon bacilli are among those microorganisms whose pathogenicity to man still remains in doubt. This group of bacteria has been studied since Widal and Noceourt¹ in 1897 described as paracolon bacillus a slow lactose-fermenting strain isolated from a patient with gastro-enteritis. However, only recently were systematic investigations undertaken pertaining to the biochemical characteristics and antigenic structure of these organisms as well as to their relationship to other species and genera. In spite of these studies, various authors still differ in their opinion regarding the exact definition and classification of paracolon bacilli. Sandiford², for instance, considers as paracolon bacilli organisms which fail to ferment lactose or ferment this substrate atypically. Topley and Wilson³, on the other hand, in their outstanding textbook, "Principles of Bacteriology and Immunity", state that non-lactose-fermenting gram-negative bacilli should not be included in the paracolon group. According to Stuart, Wheeler, Rustigian, and Zimmerman⁴, the paracolon bacillus group includes gram-negative bacilli which fail to ferment lactose or ferment it atypically. The paracolon bacilli, according to these authors, may be divided into three groups, namely (1) the paracolon *Aerobacter*, (2) the paracolon *Escherichia*, and (3) paracolon intermediates. An excellent review on coliform bacteria was published recently by Parr⁵.

Between May 15 and December 31, 1943 paracolon bacilli were isolated from the feces of 49 infants and children. An attempt has been made here to correlate as far as possible the presence of these organisms in the intestinal tract and the disease of the patients. The results of these studies are herewith presented.

The methods used in the isolation of enteric, aerobic, gram-negative bacilli has been described elsewhere⁶. It suffices to mention here that the feces were cultured on Endo, MacConkey, SS (Shigella-Salmonella), and DC (desoxycholate-citrate) agar, as well as in the enriching fluid of Bangxang and Eliot⁷. After 24 hours incubation at 37°C. subcultures were made from the enriching fluid on Endo or MacConkey agar. Colonies which failed to ferment lactose within 24 hours at 37°C. on any of these solid culture media were fished and studied biochemically. It was shown⁸ that both SS and DC agar allowed the isolation of paracolon bacilli from a greater number of stool speci-

mens that did Endo and MacConkey agar. Enriching fluid proved to be somewhat less efficacious for this purpose than SS and DC agar, but was better than Endo and MacConkey agar. The vast majority of strains isolated from patients failed to produce acid or acid and gas from lactose even when the incubation period was extended over a period of three weeks. Only a few strains fermented lactose slowly. All strains produced acid and gas from glucose. Anaerogenic strains are not included in this series.

The 49 patients whose clinical and bacteriological data are presented in this communication may best be divided into three groups. The first group is comprised of 39 cases suffering from diarrhea and harboring paracolon bacilli in the intestinal tract. The second group includes 6 patients without evidence, but with history of diarrheal disease. Four patients without evidence or history of diarrhea make up the third group. From all these patients paracolon bacilli were recovered. The pertinent data with respect to age, clinical diagnosis, and outcome of the illness are summarized in Tables 1 to 4.

Of the 39 patients with diarrheal disease 25 did not carry in the intestinal tract any pathogenic or potentially pathogenic enteric bacilli other than members of the paracolon group (Table 1). In the remaining 14 cases, aside from paracolon bacilli, enteric microorganisms such as paratyphoid or dysentery bacilli were also recovered from the feces (Table 2).

Two of the 25 cases presented in Table 1 died. The others recovered from the diarrheal disease. The post-mortem examination in one of the fatal cases revealed the presence of enteritis. Permission for autopsy was not obtained in the other.

The age distribution of these 25 patients with diarrheal disease is of considerable interest: Twelve were less than 3 months old; seven ranged in age between 3 and 6 months; three were between 6 months and 1 year old; one between 1 and 2 years; and only two above 2 years. It is evident, therefore, that the majority of these patients with diarrheal disease carrying paracolon bacilli in the intestinal tract were infants. In order to evaluate as far as possible the cause of the diarrheal disease it was considered necessary to determine how many of the patients in this group suffered from primary diarrhea and how many from diarrhea secondary to, or associated with, other illnesses. It was found that only 6 of the 25 patients were admitted solely because of the diarrheal disease. The other 19 patients suffered from other diseases, such as upper respiratory infection, otitis media, per-

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tussis, septicemia, impetigo. These cases, therefore, may be regarded as suffering from parenteral diarrhea. A few patients presented no evidence of infections outside the intestinal tract (congenital malformations, convulsions of unknown etiology). The question as to whether or not paracolon bacilli can be considered as incitants of the primary or secondary diarrheal disease will be discussed.

Fourteen patients suffering from diarrheal disease harbored, aside from the paracolon bacilli, pathogenic or potentially pathogenic enteric microorganisms in the intestinal tract (Table 2). One of the patients died; the remaining 13 of the group recovered from the diarrheal disease. The post-mortem examination of

DISCUSSION

The role played by paracolon bacilli in diarrheal disease remains obscure. Some authors believe that these organisms are potentially pathogenic and may be responsible for the mild gastroenteritis. Stuart, Wheeler, Rustigian, and Zimmerman¹ made several observations which lend support to this opinion. These investigators reported that in an outbreak of gastroenteritis in an institution the same type of paracolon bacillus could almost always be isolated from both patients and the food-handlers. In smaller outbreaks of this disease usually only one type of paracolon bacillus was found. It is also noteworthy that in the experience of Stuart and his associates¹ paracolon bacilli

Table 1
Paracolon bacillus in feces of patients with diarrheal disease

Name	Age	Other potentially pathogenic microorganism	Clinical diagnosis	Outcome
I. L.	18 days		Diarrhea; congenital malformations	Died
J. L.	5 months		Upper respiratory infection; parenteral diarrhea	Improved
C. S.	3 months		Diarrhea	Improved
S. H.	5 months		Parenteral diarrhea; otitis media upper respiratory infection	Improved
M. B.	7 weeks		Upper respiratory infection; acute enterocolitis	Improved
L. L.	14 months		Diarrhea	Improved
M. M.	7 weeks		Pertussis; diarrhea	Improved
P. M.	4 months		Upper respiratory infection; parenteral diarrhea	Improved
C. J.	5 months		Upper respiratory infection; otitis media; diarrhea	Improved
D. H.	9 months		Pharyngitis; malnutrition	Improved
R. C.	4½ years		Pneumococcal septicemia + peritonitis; nephritis or nephrosis	Died
D. L.	1 month		Fissure of anus (?)	Unimproved
J. L.	2 months		Diarrhea	Improved
W. S.	3½ months		Diarrhea	Improved
S. S.	6 years		Acute enterocolitis, convulsions; upper respiratory infection; mild dehydration	Improved
E. D.	6 months		Otitis media, diarrhea	Improved
C. L.	3 months		Congenital umbilical hernia, upper respiratory infection	Improved
B. S.	15 days		Malnutrition	Unimproved
R. S.	6 weeks		Upper respiratory infection; diarrhea	Improved
L. A.	6 months		Otitis media, diarrhea; rat-bite	Improved
G. T.	8 months		Upper respiratory infection; diarrhea	Improved
C. B.	8 months		Upper respiratory infection, otitis media	Improved
J. B.	1 month		Acute enterocolitis	Improved
M. D.	3 months		Acute enterocolitis	Improved
G. H.	3 months		Encephalopathy with convulsions	Unimproved

the fatal case revealed acute hemorrhagic colitis, localized peritonitis, and marasmus. The age distribution of these 14 patients was as follows: Six were infants less than 3 months old; three ranged in age between 3 and 6 months; one was between 6 months and 1 year; three between 1 year and 2 years; and only one above 2 years of age. In 8 of these 14 cases the diarrheal disease can be adequately explained by the presence of recognized pathogens; *Shigella paradyseae* (Flexner dysentery bacillus) was present in 5 cases, *Shigella castellanii*, *Salmonella typhi* murium, and *Salmonella thompson* in one patient each. In the remaining 6 cases, aside from paracolon bacilli, either *Proteus vulgaris* or *Proteus morganii* type I was recovered from the feces. Since the pathogenic significance of these microorganisms is not yet definitely established the cause of the diarrheal disease remains in doubt.

were frequently present in almost pure culture and that a parallelism existed between the presence of these organisms and the clinical symptoms and signs. Finally, these authors reported that 4 out of 6 persons working with these strains contracted the infection. On the other hand, Sandiford² is of the opinion that the presence of paracolon bacilli in the stool is most probably without etiological significance. His investigations were carried out in Egypt. The cases reported in this communication have been presented to add to the literature on the possible pathogenic significance of paracolon bacilli.

Any attempt to prove or disprove the pathogenicity of these microorganisms is confronted with three main difficulties. Firstly, without any doubt, paracolon bacilli are encountered in persons without evidence or history of diarrheal disease. Four such cases have been observed at this hospital during the period of this

study. Secondly, the presence of these organisms in the feces in persons with diarrheal disease does not constitute adequate evidence of their pathogenicity. It is interesting to note that paracolon bacilli are more frequently encountered in the stools of patients with diarrheal disease than in those obtained from healthy individuals. In the experience of Sandiford² paracolon bacilli were present in 16.1% of stools sent for examination for dysentery and in only 8.6% of normal stools. The difference in the incidence of these organisms may indicate either that paracolon bacilli play a primary or secondary role in diarrheal disease or that they occur as saprophytes more frequently or in greater number in patients with enteric infections caused by other incitants than in normal individuals. In the series

the possible pathogenic significance of these organisms. Only then will it be possible to state whether paracolon bacilli are more often present in patients with diarrheal disease than in those of the same age group free of this illness. The results of such a study will be reported elsewhere (Neter, J. Pediatrics).

It is important to note that many of these patients suffered from diarrheal disease as well as from other disorders, particularly infections. It is therefore reasonable to assume that we are dealing in these instances with parenteral diarrhea. The pathogenesis of parenteral diarrhea is not yet completely understood. It is possible that it is due to the absorption of toxins or toxin-like substances from inflammatory lesions outside the intestinal tract. Changes in the bacterial flora of

Table 2
Paracolon bacillus in feces of patients with diarrheal disease

Name	Age	Other potentially pathogenic microorganism	Clinical diagnosis	Outcome
R. B.	6 months	Salmonella typhi murium	Acute enterocolitis; common cold	Improved
C. A.	2 months	Shigella paradyseuteriae	Common cold	Improved
C. L.	5 weeks	Proteus vulgaris	Enterocolitis	Improved
D. M.	27 days	Shigella paradyseuteriae	Acute hemorrhagic colitis; bronchopneumonia; otitis media	Died
D. M.	13 months	Proteus vulgaris	Upper respiratory infection; parenteral diarrhea; otitis media	Improved
D. K.	2 months	Proteus vulgaris	Upper respiratory infection; otitis media	Improved
N. B.	6 months	Shigella paradyseuteriae	Dysentery	Improved
J. S.	12 years	Salmonella thompson	Diarrhea	Improved
A. M.	8 months	Proteus vulgaris	Upper respiratory infection	Improved
H. B.	2½ months	Shigella castellanii	Otitis media; diarrhea	Improved
J. D.	13 months	Proteus morganii type I	Otitis media; parenteral diarrhea	Improved
R. M.	6 months	Shigella paradyseuteriae	Dysentery	Improved
V. S.	13 months	Shigella paradyseuteriae	Dysentery	Improved
T. B.	7 weeks	Proteus vulgaris	Malnutrition; diarrhea	Improved

of 49 infants and children presented in this article 39 were suffering from diarrheal disease. All 49 carried paracolon bacilli in the intestinal tract. In 25 of these 39 cases no other enteric pathogens could be isolated. In the remaining 14 cases, however, other pathogenic or potentially pathogenic organisms were recovered, namely, various paratyphoid bacilli (*S. typhi murium* and *S. thompson*), dysentery bacilli (*S. paradyseuteriae* and *S. castellanii*), *Proteus vulgaris*, and *Proteus morganii* type I.

The pathogenicity of typhoid and paratyphoid has been established beyond doubt, that of *Proteus vulgaris* and *Proteus morganii* type I is yet to be determined. (Neter and Bender⁹). Of the 14 cases suffering from diarrheal disease and harboring paracolon bacilli, 8 also harbored *Salmonella* and *Shigella* organisms which may adequately explain the cause of the disease.

The occurrence of paracolon bacilli in infants and small children with diarrheal disease raises the question as to whether or not individuals of that age group are less resistant toward paracolon bacilli than older children and adults. Of the 39 cases with diarrheal disease 33 were infants one year of age or less. It is necessary, therefore, to determine the incidence of paracolon bacilli in feces of healthy individuals of different ages before conclusions can be drawn regarding

the intestine may occur secondarily. The role played by this altered bacterial flora in the diarrheal disorder is not known. No statement can be made at the present time whether the presence of paracolon bacilli in the intestinal tract of infants and young children with parenteral diarrhea contributes to the development and continuance of the diarrheal disease.

The third difficulty confronting any attempt to evaluate the significance of paracolon bacilli as possible incitants of diarrheal disease is the now established fact that not all patients develop specific anti-bodies against infecting microorganisms. In a series of 8 cases of enteritis, colitis, or enterocolitis reported recently (Neter and Farrar¹⁰), for instance, specific agglutinins against potentially pathogenic microorganisms present in the intestinal tract (*B. proteus* and *B. morganii* type I) could not be demonstrated in the serum of these patients even several weeks after the onset of the illness. In rabbits, however, two representative strains upon intravenous injection readily engendered agglutinins, indicating that these organisms did not lack in antigenicity. More conclusive than this observation is the report that patients with diffuse peritonitis or abscess formation following appendicitis may fail to produce agglutinins against aerobic, gram-negative bacilli present in the purulent exudate (Neter and Milch¹¹). Therefore, the absence of agglutinins against paracolon bacilli would not necessarily disprove the

pathogenicity of these microorganisms.

The present-day knowledge of the possible pathogenicity of paracolon bacilli may be summarized as follows: (1) These organisms may be merely saprophytes; they may be encountered in the feces of individuals who do not present history or evidence of diarrheal disease, as in the four cases presented here. (2) Paracolon bacilli may be present in the intestinal tract as harmless organisms in patients with diarrheal disease caused by enteric pathogens or other incitants

tended to 3 weeks.

3. Thirty-nine of the 49 patients presented evidence of diarrheal disease during hospitalization. Of these, 25 carried paracolon bacilli but no other pathogenic or potentially pathogenic enteric microorganisms. In the remaining 14 cases, in addition to paracolon bacilli, other enteric organisms were present, namely, paratyphoid or dysentery bacilli, *B. proteus* or *B. morganii* type I. Eleven of these patients were admitted to this hospital solely because of diarrheal disease, whereas in

Table 3

Paracolon bacillus in feces of patients with history of diarrheal disease

Name	Age	Other potentially pathogenic microorganism	Clinical diagnosis	Outcome
R. N.	3½ years		Infantile paralysis; upper respiratory infection	Improved
C. W.	2 months		Observation because of history of diarrhea	Improved
V. S.	8 months		Upper respiratory infection	Improved
P. S.	10 months		Common cold; bronchopneumonia	Improved
W. S.	1 year		Multiple burns (right arm)	Improved
J. K.	12 years	<i>Shigella schmitzii</i>	Subacute appendicitis	Improved

(parenteral diarrhea). It is doubtful, however, if the explanation of Sandiford² holds true that the greater incidence of paracolon bacilli in patients with diarrhea is due to a general increase in the total flora of a disordered bowel. (3) Paracolon bacilli may be associated with enteric pathogens and play a secondary part as incitants of diarrheal disease. (4) Paracolon bacilli may be the primary cause of diarrheal disease in certain susceptible individuals, particularly in infants and children. Moreover, there is fairly conclusive evidence that these organisms may cause gastroenteritis (laboratory infection) and even outbreaks of this disease particularly in institutions (Stuart and associates³). Further studies are necessary before it is possible to

the remaining cases hospitalization was required because of other disorders such as upper respiratory infections, otitis media, etc. Three patients of this group died; the others recovered from the diarrheal disease.

4. Six patients harboring paracolon bacilli in the intestinal tract were admitted without evidence, but with history of diarrheal disorder.

5. Paracolon bacilli were present in the intestinal tract in 4 individuals who presented neither history nor evidence of diarrhea. A report on the incidence of paracolon bacilli in the feces of healthy infants will appear in the Journal of Pediatrics.

6. The majority of patients harboring paracolon bacilli were infants and children under two years of

Table 4

Paracolon bacillus in feces of patients without evidence or history of diarrheal disease

Name	Age	Other potentially pathogenic microorganism	Clinical diagnosis	Outcome
J. B.	3 weeks		Prematurity, convulsions (cause unknown)	Improved
E. R.	5 years		Admitted for observation no diagnosis	Improved
I. S.	14 years		Neurosis with symptoms of intestinal pain	Improved
A. C.	5 weeks		Pyloric stenosis	Improved

establish or disprove the etiological significance of paracolon bacilli in enteric disorders.

SUMMARY

1. Clinical and bacteriological data are presented on 49 infants and children harboring paracolon bacilli in the intestinal tract.

2. All strains of paracolon bacilli isolated from these patients produced acid and gas from glucose, and the majority of them failed to form acid or acid and gas from lactose even when the incubation period was ex-

age. Of the 49 individuals, 31 were less than six months old; 35 one year or less, and only 6 were older than two years.

7. The significance of paracolon bacilli as saprophytes or potentially pathogenic microorganisms acting as primary or secondary incitants of diarrheal disease is discussed.

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Caecum (Typhlon) with Ascending Colon and Part of Transverse Colon Considered as a Chamber: Superior Colic Ventriculus (Holotyphlon)

by

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BEFORE writing upon the nature of disease associated with this part of the Alimentary Tract, or even thinking of possible allergy, of vitamin (imbalance) (or of toxic) absorption, the structural values of the area require study.

It seems probable that fluids (gases and liquids) are here removed and retained by the body, rather than allowing loss. Also, in spite of notions that in Man little real nutritive absorption takes place in this area, we see the portal system richly connected.

A. Chauveau, S. Arloing, and George Fleming (1) state: "The caecum serves as a reservoir for the enormous quantities of fluid ingested by herbivorous animals. The greater part of this fluid in its rapid passage through the stomach and small intestine escapes the absorbent action of the villi and accumulates in the caecum, into which it may be said to wash the alimentary mass it comes in contact with, it thus dissolves the soluble and assimilable matters this mass may yet contain and so favors their entrance into the circulation, through the immense absorbing surface formed by the mucous membrane of the large intestine.

"The aliment undergoes still further change, and digestion is completed in this viscus (caecum) principally in the Herbivora."

In Man, we know that the ileocecal valve is closed by distention of the Caecum. This delays entrance of matter from the ileum. Gas, or soft mushy material filling the caecum must be passed onward before more material is received from the small intestine. In many animals (2) the exit from the caecum (horse) is about two inches only from the ileocecal valve, and the orifice of exit to remainder of colon is very small. Slow maceration and delayed passage is needed here, in animals, and in Man, but in Man the delayed passage

occurs from ileocecal valve to mid-colon, or to splenic flexure. Exact recognition of the structural entity of this Superior colic ventriculus (in man) will be desirable, and its physiology and pathology will then be obtainable.

The stomach (ventriculus) is developed by dilatation of the prima via. It then rotates. So, also, the caecum dilates, and then rotates.

The Lien (spleen) is produced in the posterior mesogastrum. There may be small accessory spleens, elsewhere as in liver (Hepar) and in mesentery. At the caecum (typhlon) we find the node of Lockwood (3) (4) (5) in the ileo-appendiceal angle. The absence of villi in Intestinum crassum is significant. It is stated they occur on the ileal side of the cusps of the ileocecal valve, and default on their caecal faces.

We may inquire whether a defect in digestion of the small intestine causes a mass in the caecum of an improper character, which by its greater delay, further holds up more material from entering through the ileocecal valve, or whether defective digestion in the caecum is the real cause of this delay.

When the digestive action within the caecum is in abeyance it and much of the colon, may be no more than a channel of exit (called a "sewer"). However, that its normal state is not merely a channel of exit may be held true in this study. The appendix, too, as a special area may be actively valuable (6).

Further, in comparative anatomy, the area of caecum (typhlon) extends beyond the level of the entry (ileo-caecal valve of Baulhin). But in human anatomy we term the "ascending" colon all that area from the level of the valve, improperly, it should be noted, as the caecum (Superior colic ventriculus) extends as far as a relative narrowing. We find the "descending" colon empty, usually, after death (7) showing the limit of the chamber in the area of retained material.

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No attempt can be made to lay down general routine study of the upper colon. The caecum is singularly isolated. But the use of charcoal, in powder, is sometimes excellent, it acts on gases, and putrefying matter. Combine some digestive enzymes and a fractional dose of Potassium nitrate: enema clears out lower bowel, and it is wise to wait the appearance of charcoal in the feces before purgation. Essence of pepsin, in frequent doses will prove a valuable associated treatment. And at the proper intervals, give citrate of potassium, combined with syrup of lemon and a little glycerin in water. The continued exhibition of carbo lignis powders (charcoal) every two hours gives results, until a special general treatment can be determined.

The problem of gas in the caecum and colon indicates the real nature of the digestive default. In analysis, the function of ascending colon differs from that of descending colon (8).

First, the location of this chamber, *Holotyphlon*, is here considered, and, secondly, a determination of its activity.

In general, clinicians are able to locate the Pyloric valvula, and the Ileocecal valvula, by listening to the sound of the sudden outflow. To elicit this sound, like a stream squirting from a nozzle, for an instant, give a drink of water, or milk, and place the ear over the probable area, the ear resting upon a thin silk or cotton handkerchief upon the bared skin of abdomen. A sound like "slish" will occur, soon after swallowing the fluid, heard at the pyloric area.

It is very interesting to observe that in a short interval, a succeeding ejection takes place at the ileocecal orifice.

Several factors may account for lack of success in noting this sound, many will occur to mind: but overloaded stomach, or greatly distended caecum, may, equally, interfere.

The singular interest in this simple procedure, is that when obtained, we have positive evidences. Many reasons have been given for failure of the ileocecal valve to operate in close sequence, reflex interference, or individual dilatory response. In a day when no x-ray existed, such simple procedures were much admired. And, now, many additional conclusions can still be available, with a richer laboratory equipment. In fact, careful study of the abdomen includes auscultation at several areas, for borborygmi, splashes, and other evidences of intestinal action. At different periods, according to amount of food taken, or interval, we can still employ to advantage the auscultatory method. Giving liquids at regulated times in this connection will enlarge the technique.

The ileocecal valve is often described in texts as directed toward the right body flank. The terminal ileum tends to the right. But dissections of over a thousand caeca (human) show the frenula are placed to exert a transverse tension, the right frenulum passing across the dorsal wall of the caecum. The ostium really opens to the front, although the caecum extends ventrally upon the ileum. The posteromedial taenia of the ascending colon may split to receive the terminal ileum, may pass ventrad to it (about an inch and a

half proximad to the ileocecal orifice (Tulpius, Bauhin, Young) or, usually, extends dorsad to the terminal ileum, (which is one of the reasons authorities suppose the orifice points dextrad). From the longitudinalis of the ileum a muscular band separates off to pass to the base of the processus vermiformis (epityphlon) and joins the taeniae which enclose the root of the epityphlon. Normal peristalsis may depend upon this arrangement.

The third portion of this note now turns to the actual relations, human and comparative.

Analysis.

A previous note (Bulletin, N. Y. Medical College) (6) on the consideration of the Appendix (Epityphlon) as functioning, at least in part, in receiving and absorbing gases from the intestinal canal, may be further extended to include the idea that the Caecum in combination with the Ascending Colon and the Transverse Colon as a chamber, the *Holotyphlon*, together, are important in removing not only liquid matter, but gaseous products, of essential value.

It is evident that during digestion we rarely pass flatus per anum. Unless this flatus be retained, some chemical loss would occur.

The production of solid or semisolid faeces suggests changes in or absorption of the fluids.

In the bird, such as chicken, there is practically no length of large intestine (*Intestinum crassum*). The chicken possesses two caeca (called paired) about one inch from the anal orifice. These caeca are dilated and sacculated, with lumen at entrance greatly restricted. They are rarely filled with solid matter. In the unborn chicken they are well developed. The sulfur in the yolk would, possibly, create gas which is reabsorbed in the caeca, for if emitted in the egg-shell compartment, this gas would suffocate.

Sulfur in appreciable quantity, in man or in any animal, would be a loss to the body metabolism. If reabsorbed, it could be used again and again.

The gas in a dilated intestinal canal may be an important element. I have often wondered what gas occupies the intestinal canal, when dilated under ether anesthesia. How is it produced?

The Processus vermiformis has been greatly studied. That it is placed just at a point to receive gases during digestion, can be noticed and its structure is one which maintains a lumen.

The orifice (Gerlach) is guarded by a crescentic flap, around which taeniae are invested to sustain the relation, and a longitudinal band of muscle from the ileum is carried to the orifice of the Epityphlon.

Various authorities have written concerning the comparative uselessness of what they term the "sewer," (Large intestine).

We can realize that in Herbivores (Fleming and Chauvaud) the Caecum has a period of second digestion (so that it acts like a stomach in being a Chamber). In man, we do not definitely describe a period of delayed movement of food while in the Caecum and upper colon. After digestion has occurred in man in the small intestine (*Intestinum tenue*) there will remain an amount of material which is required in suc-

cessive chemical processes, and these elements are regained from the flow toward exit, before an important loss to the body can occur. I suggest "Holotyphlon" as a name for this chamber, as far as the splenic flexure.

The Caecum, by many authorities exhaustively examined, in the cat (Reichart and Jennings, Chauveau) shows a constant lymph node, termed by Chauveau a definitive "Peyer's" patch. This node (Lockwood) (5) in man is constant within the peritoneum, forming the inferior ileocecal fossa, just behind the bloodless fold of Treves. But such a lymphatic node in the Ox or the Horse is denied generally. The Processus vermiformis (W. R. Campbell) is a highly lymphatic structure, excessively so, related to tonsillar tissue, which partially explains caecal involvement in respiratory ailments. Bailey says of the Vermiform appendix that the lymph nodules are the most conspicuous feature, and lie mainly in the submucosa; the nodules are oval, or spherical or distinct and arranged like a Peyer's patch, with apices and base. The muscularis of the submucous tissue may pass through the superficial portions of the nodules. The processus, therefore, may resemble terminal intestine tenue. Fluids of the caecum tend to be subjected to a form of the digestive activity, further, and in the herbivores, the caecum (Chauveau) (1) operates as a chamber of digestion, which, evidently, now that the small intestine has digested and assimilated certain elements, continues the activity in a way which could not have occurred in the stomach. The alimentary canal, (a succession of canalicular treatment of food, and of chambers), shows elaboration directed towards retention at various stages. Gases are not desirable in the canalicular portions, except to dislodge hard masses, possibly. In the chambers there will occur more opportunity to collect, alter and reabsorb gases. In Man, speaking generally, the Processus vermiformis is called rudimentary, recessive or of little importance. It should be regarded as a highly specialized area. Nevertheless, considered with the caecum, and in view of the fact that this narrow tube is not produced fully in many human beings, or is absent (30 instances), (9) (10) it is assumed it has relatively little to do. But gases may readily enter it. Its restricted lumen allows the approach of gases to the wall. Its tissues have some affinity for the lymphatics of Nose and Pharynx.

In the herbivores, Chauveau observes that the lumen of exit from the caecum to colon could scarcely be relatively smaller. This insures the retention of fluids, as well as of solids during caecal digestion. Chauveau describes the four longitudinal muscle bands of the caecum as present in only its middle portion, disappearing toward each extremity. At the small orifice of the caecum leading to the colon, these four longitudinal bands reappear, connected at the ostium, and follow the colon, so that there is an arrangement of caeco-colic orifice similar to that presented by the converging taeniae, in man, at the orifice of Gerlach's valve into the processus vermiformis, one suited to control of ostium, and to conveyance of muscular action in peristalsis. This similarity should not lead to the idea

that the human "epityphlon" represents the herbivore caecum. But gives analogy, (rather than homology) in part. John B. Deaver used to deny acute "Typhilitis" in Man, at a time (1898) when the subject of Epityphlitis was a young and more or less improvised discussion. Gas readily passes into the Colon and everyone was familiar with the colic, and distention, in the large intestine, especially as in children. The peculiar part played by the Epityphlon, even yet not clearly delimited, was associated with cases of impacted "orange seeds." Some of these objects turned out to be merely oval inspissated faecal particles probably due to failure of the "succus entericus." (E. T. Reichart and others). This inspissation in man, may give rise to hard plates held by the caecal mucosa, and causing ulceration in areas. *This reduces the area of fluid reabsorption, and the treatment of liquids and gases, and may be associated with a retrograde change in the walls of the appendix.* (11) In man, in contrast to the lower forms here compared, the reduction of lumen of the large intestine is deferred to the area of the splenic flexure.

This significant fact shows that caecal digestion, gas, liquid, or solid, such as it may be, in man, is allowed all the area of the caecal (non-appendiceal) part of the large intestine, prolonged through the ascending and the transverse colon, but not fully continued into the descending colon (Such an anatomic construction further sheds light, upon the relevance of *epityphlic reabsorption of gases*). In this elongated chamber, the Holotyphlin, we see a true caecal stomach. Studying the functional valve (mid-colic) attributed to Cannon, who definitely found such physiological evidence in experimental animals, we see an area probably one of change in the parasympathetic distribution (the sacral fibers distributed upward from the inferior mesenteric arterial tree). One cannot deny this arrangement continuing the caecum functionally, and the narrowing of lumen at, or near, splenic flexure is practically constant. Such as it be, fluids, (liquids and gases) are definitely restricted at the splenic flexure and functionally forced backward towards the orifice of the Epityphlon, since they usually do not re-enter the small intestine. The alkaline reactions of the small intestine may change into acidity in the large intestine. Such conditions assume a separate phase, accompanied by concomitant anatomy. And the upper colon is supplied by superior mesenteric (Flint's phylogeny rule). In addition to the very great reduction of lumen at the splenic flexure, there is a pronounced angulation, with a hip at the angle. Distention occurs proximad to this. [By the canalicular and chambered alternations previously described here, in some persons there is a dilatation called the Omega loop (Piersol, 1895). This region of iliac colon occasionally becomes of great size, and terminates at the Pelvic sphincter (O'Beirne). Needless to discuss this development.] It is enough to describe that of the Caecum in relation to appendix and to state plainly the apparent value or function of its mechanism in relation to gases, and continued absorption, although modified, as far as the splenic flexure.

Summary

Having shown, in man, and in comparative animal types, the area which may be called that of the Superior Colic Ventriculus (*Holotyphlon*) it is evident that the Physiology and the Pathology of this portion of the alimentary canal is a very important matter; (to surgeons, dealing with the "acute abdomen," less immediate interest in previous conditions is possible).

A better handling of the colon, however, before acute or chronic lesion develop may become possible, especially if we are directed to the area as a definite region of slower progress. The study of faeces as a routine affair is still not common. Also, in acute respiratory conditions the colon demands attention. (12)

Disturbances lower in the alimentary tract cause re-

flex changes higher (Edward Martin). Constipation, obstipation and various excretory functions are probably concerned with difficulties in this region. Those who have seen animals (horses or oxen) become paralyzed from improper feeding, know as well as all veterinarians do, what this nerve collapse implies. In man, from childhood to old age, extreme conditions develop. Because a classical tradition denominates the large intestine (colon) as a simple entity, we have omitted to discriminate among its actual physiologic subdivisions, as we might. (7)

This note, resulting from over a thousand careful dissections, could be followed by considerable detail, known it is true to all of us, but as yet quite in its infancy as to medical application; in conditions of colon complicating other ailments, especially.

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Why the Failures in the Treatment of Allergy

by

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THOUGH that group of physical phenomena which we now somewhat loosely designate as *allergy* has been known to scientists ever since the days of Louis Pasteur, the phenomena themselves, as well as clinical features with which they are associated, are of comparatively recent recognition. Hans Zinsser's "Harvey Lecture," delivered in 1914, was an eye-opener to even the most advanced practitioners of medicine, and it was a long time before the results of the investigations he and others had carried on, began to show doctors how many of the common ailments whose etiology had been explained, might be controlled and abolished by nothing more complicated than dietary limitation.

* It was while working in the Massachusetts General Hospital in 1914, many months before Zinsser spoke, that I came in contact with a man of 40, who had been attending the clinic for 6 years, vainly seeking permanent relief for attacks of sneezing, with alternate blocking of the nares, and discharge of a copious watery secretion. He was a baker by trade, but when questioned as to whether the attacks were more frequent, or worse, while at work, he replied he was "so bad all the time" he noticed no difference while in the bakery.

Other physicians who had previously treated him had, upon receiving this reply, abandoned the idea of an occupational disease. But inasmuch as so many other lines of treatment had failed, I resolved to attempt something entirely different. At my request he brought me samples of all the flour used in his bakery. There were three of these samples—what he called a "high" grade, a "low" grade, and a "regular" flour. Preparing a separate paste from each sample, using water only, I made four "vaccination" scarifications over the biceps area of one arm, inoculating three with the three flour pastes, and keeping the fourth scarified spot as a control. Within three minutes, reactions began in all three inoculated areas—there was rapidly increasing redness and swelling and intense itching, with a wheal-formation soon reaching 2 cm. in diameter. The control spot remained unaffected.

The intense local reaction reached its maximum in about thirty minutes, thereafter decreasing to disappear entirely after an hour and a half. There was no constitutional disturbance of any kind. I told the man to take a vacation from the bakery and to omit all bread from his diet. He followed directions and all his nasal symptoms disappeared as if by magic. Permitted to return to work, but to eat no bread, his symptoms

where I had climbed by slow, laborious steps. I was ordered (not requested) to instruct him and a group of his friends in the preparation of extracts and tests, and all the procedures of the clinic. Rather than do this, I decided to give up the clinic entirely, despite the warning vouchsafed by those who sought to replace me, that my departure would "leave an awful stink."

I have related this personal experience at length because it illustrates a point of view in regard to the detection and treatment of allergy, which the medical profession in great part, still maintains after the lapse of a quarter century. This might be termed the "any-fool-can-do-it" attitude, and it is to this—quite as much as lack of cooperation on the part of patients and referring physicians—that the many failures in the treatment of allergy are to be attributed. While I still had my clinic at the Massachusetts General Hospital, a physician from a distant city who was doing post-graduate work there sought an invitation to visit me, which I, of course, extended. Soon after he informed me he was returning home and would not have the time to inspect the clinic. A year later a patient consulted me who had been "tested" by this same out-of-town practitioner. Both arms were permanently scarred but she reported "no benefit" as a result of the tests. I had a similar experience with a child of nine years whose arms had been terribly scarred by a practitioner who had not even *thought of visiting* a clinic where the test-procedures and therapy of allergy had been scientifically worked out. A single test—on another body surface—revealed the cause of the child's asthma, and dietary regulation promptly relieved her. The wonder is that the general public still has faith enough, after such barbarous displays of ignorance by doctors supposed to know what they are doing, to persevere in seeking competent treatment.

Choice of Testing Surface.—While the anterior surface of the arms is the best region for making the cutaneous tests, when for any reason this is not available, the legs, abdomen, back and chest, in the order given, must be chosen. The arm surface may be scarred by previous improper testing, as already mentioned; it may be scarred from other injuries (cuts, burns, etc.), or display psoriasis tattooing, eczematous excoriation, or the arm may be ankylosed in a flexed position from arthritis or injury. In testing a patient for the cause of giant urticaria and angioneurotic edema the forearm could not be used because when the examiner's fingers were drawn along the skin surface a marked dermatographic reaction ensued.

Variation in Skin Types.—Though all skin tests should be carried out with the least possible trauma, there is a great difference in the structure and quality of the skin of normally healthy people, and without knowledge of these possible variations, no one should attempt to make or interpret the results of skin tests for protein sensitization.

When the skin is normally elastic, it feels "alive" and offers moderate resistance to pressure. On very thin skin only the slightest pressure should be exerted, while the very thick, on the other hand, will require

considerable pressure in making the incision. Sometimes the skin will offer no resistance and gives one the sensation of cutting lead, found usually in the aged, especially if emaciated. As bleeding washes out the test substance, and forms a coagulum with the extracts used, it must always be avoided, and it must be kept in mind that pregnant women are very likely to bleed easily.

The incisions should always be made in a regular pattern, so as to be easily read. The proper performance of this routine is only possible after extended practice and close observation, for it is by no means "as easy as it looks." The materials used are likewise important, and many failures in diagnosis are due to improperly prepared extracts. I still make my own, and thus make sure that I am employing the correct substance for each individual. Human beings are seldom built on a "stock" pattern.

Interpreting the Tests.—If skill and experience are required to make the tests, how much more are they essential in interpreting them! One hears patients—and physicians, too—assert they were "sensitive to everything"—the control test showing as large a wheal as the others—nothing can be interpreted on "a hypersensitive skin." But with intelligence and care, even in urticaria or angioneurotic edema cases, the reactions can be correctly interpreted, as I have repeatedly proved, when the patient obeyed instructions to eliminate the offending proteins from environment or diet, and witnessed prompt remission of all symptoms.

"Hay Fever" Reactions.—Since it has been determined that not hay, but the rag-weed pollen that floats in the air at haying time, is usually responsible for hay-fever, physicians calling themselves allergists have ceased to consider any other substance as a possible cause for that particular anaphylactic manifestation. On the other hand, if a patient who has never had hay-fever reacts to any pollen extracts, they are prone to call these "false reactions," and perhaps condemn all therapy against allergy as useless. When such a patient comes under my care, I look for other manifestations—such as cough, asthma, or conjunctivitis and other symptoms—but at the same time inform him that he is sensitive to certain pollens and should avoid them, lest he develop hay-fever later. And in several instances precisely this has occurred. Some patients sensitive to pollens prevalent in August and September, will experience no difficulty in June and July at the time they first apply for treatment. Yet they will react to pollens prevalent in the earlier months. Most physicians observing such a reaction will pronounce it "false." In my own experience such a patient—I have in mind one who gave a ten-year history of hay-fever in August and September only, but reacted strongly to June-July pollens—may become *sensitized* during the earlier part of the summer, but react only on the *second dose* later in the season. After a time the earlier dose will produce an anaphylactic reaction, as was observed in the earlier days of serum treatment. This was what happened to the patient mentioned above, who reacted to timothy and red-top and to rag-weed as well. The following year, when no treatment

against rag-weed had been given, hay-fever appeared in June. Such "false" reactions should never be ignored, for their proper interpretation may save the patient much discomfort—both physical and economic.

"Rizarré" and Abnormal Wheals—Occasionally one meets an individual who reacts to a skin test, applied in the usual manner, in such an abnormal way as to strike terror to the heart of even an allergist of wide training and experience. In the early days of my clinic at the Massachusetts General Hospital, an incensation on the arm, just below the antecubital fossa, produced two red lines which ran up the arm, on either side the biceps muscle, to the shoulder. The lines appeared two minutes after the test substance was applied, and reached the shoulder in eight minutes, continued to increase in the intensity of their color for twenty minutes, then gradually faded, disappearing completely in about forty minutes, all without the slightest pain or discomfort to the patient. No matter how often the test was repeated, the red lines appeared and ran their course in precisely the same manner (this patient was used a number of times for demonstration at the clinic). I have sometimes seen wheals with pseudopodia of different shapes and sizes, often branching in different directions, though most often the pseudopodia will run down the slope of the arm, whatever the chances to be, seeking a lower level along the line of least resistance.

Reasons for Failure in Testing and Treatment for Allergy—The reasons why so many failures in the tests and treatment for allergy continue to take place, are almost as varied as the viewpoints of those who report them. I could fill a book with incidents illustrating these causes of failure and pointing out how they could have easily been avoided. A few briefly summarized examples must suffice:

A. THE PATIENT DOES NOT KEEP TO THE DIET PRESCRIBED.

1. Woman complaining of arthritis and arterial hypertension, with weakness and exhaustion, after testing was placed on appropriate diet. Disappearance of pain and joint-swelling, recovery of strength and energy, and a 50 mm. reduction in systolic pressure promptly resulted and persisted for 3 months. Thereafter all symptoms returned, and upon questioning, the patient gave the reply quoted earlier—my instructions were given too earnestly. No further appointment was given this patient.

2. Three months prior to consulting me, a woman had suffered a severe tonsillitis, following which she had been subject to brief, but continually recurring attacks of unconsciousness, 20-30 daily, lasting from 20 seconds to a minute. Blood pressure, systolic 250, diastolic 140. My diagnosis was temporary spasm of cerebral artery, induced by allergy as revealed by skin testing. An appropriate diet immediately relieved the unconsciousness attacks and they did not recur for four months while the patient remained under observation, the blood pressure likewise descending to 165/90. She then went to the seashore and two months later the family physician telephoned the unconsciousness

attacks had returned. He maintained the patient was still "on" the diet, but both physician and patient failed to understand the importance of strict adherence to the diet. With elimination of all foods to which she was sensitized, I am certain she would have had complete relief.

3. A patient who had undergone all standard measures for relief from arthritis, was tested and placed on the diet indicated by the tests; in 2 weeks marked improvement; in 4 weeks complete relief of all symptoms which persisted for 3 months. Patient then took a motor trip during which she ate forbidden foods for one week, but suffered no return of the arthritis. She continued to disregard her dietary limitations for one week while at home, and for a third week while on a second motor trip. Three days after the second return she experienced all her previous pains, and was advised by her husband to return to me at once. She replied she was "ashamed" to do this, but would at once return to her diet. Three weeks later she came to me quite free from all symptoms, and related her story. But for the cooperation of the husband, this case would have proved another "failure."

4. A woman with a very severe eczema of long-standing, who had tried every form of treatment without relief, came to me as "a last resort." In addition to the dietary regulations indicated by the skin tests, I cautioned her to avoid certain flowers. Though she did not follow instructions very strictly, there was marked improvement in the skin-condition within 2 weeks. Then she carried some of the forbidden flowers and remained in contact with them for many hours. There was an immediate severe eczema reaction, and complete discouragement on the part of the patient, who declared "Nothing will do any good!" I pointed out that improvement had taken place, despite two infractions of the rules, and she consented to following all regulations implicitly for one week more, after which—if no better—she would be entitled to condemn the treatment. Though I had doubts of her fortitude, this woman kept her word, and was rewarded by complete relief of all her symptoms.

B. DISBELIEF OF OTHER PHYSICIANS, OR UNETHICAL INTERFERENCE WITH PATIENTS UNDER ALLERGIST'S CARE.

1. During the rag-weed pollen season, a man consulted me for dermatitis of hands and face, including the conjunctivae. He reacted not only to pollen but also to certain foods, so control of both diet and environment was prescribed, and desensitization treatment instituted. He was relieved of all symptoms for that season, but the following year neglected to renew his precautions under my direction. When he accompanied his mother-in-law who had asthma, to the office of another allergist, this man persuaded my patient to let him make a skin test with rag-weed pollen. This allergist's test was negative, but because the patient told of his experience with me the previous year, the allergist referred him for immunization to the mother-in-law's physician. But when the rag-weed

blossomed that year my patient's "hay-fever symptoms" in skin and eyes returned in full force. He returned to "where he had gotten help before," once more reacted to the tests and received the proper treatment, which was completely successful. His mother-in-law's treatment for asthma by the other allergist having "failed," she too, underwent the proper tests, and I was able to afford her complete relief. Here we have two "failures" in the treatment of allergy, and two gross violations of medical ethics—coaxing a patient who had announced himself as previously under my care, to undergo a skin test, and then supplying a third physician with desensitizing material to treat this patient, though this third physician was not the patient's family doctor.

2. An even greater violation of professional ethics occurred in another case, that of a man suffering from general depression, and exhaustion with great weakness. Excellent results were obtained on the diet indicated by the skin tests, which had also revealed the patient's sensitivity to tobacco smoke, which he complained caused headache, sore throat, and cough. This man made excellent progress for three months, but was then taken acutely ill, and seen by another physician. This doctor was unable to make a diagnosis, but informed the family that I had "poisoned" the patient with my tests made three months previously. Notwithstanding, he called in a third physician to make a new set of tests. This other allergist failed to find any sensitization, whereupon my methods and diagnosis were condemned. But the housekeeper having noticed that the renal symptoms for which I had previously given some medication, were once more in evidence, the patient himself began to take this medicine, and immediately recovered. I afterward learned that all of the four consultants who gathered at this man's bedside, smoked during their conference, ignoring his allergic reactions. Yet not one could tell what ailed the patient!

3. An orthopedist sent his wife to me for treatment of vitiligo. I informed her that the existing discoloration of the skin could not be removed, but the process could be arrested by following the diet indicated by the results of the skin testing. Blood pressure was systolic 100 and diastolic 70, but I told the woman that faithful adherence to the diet usually corrected abnormally low pressure. When she reported my findings to her husband, he at once sent her to a cardiologist, and decided that the diet prescribed was "too radical a change" and would prove a "shock to her system" if I did not modify it. During the three weeks before she returned to my office she failed to follow instructions and so was no better. Because of the husband's unethical attitude, I declined to give her a further appointment, and this orthopedist has ever since condemned me, my work, and skin tests in general.

Other doctors have sent their patients elsewhere and received negative reports so regularly that they have lost faith in any sort of diagnosis or treatment for allergy. When sent to commercial laboratories this happens so frequently that both patients and referring

physicians become disgusted and call it a "simple waste of money"—as indeed it is. Others decry the whole matter as "nonsense." A college Freshman told the examiner that he had been my patient, and had been proved sensitive to certain foods and pollens. He was told to "forget it"—that the examiner himself had a food allergy, but ate whatever he liked and disregarded the reactions.

4. Early in my experience in the M.G.II. clinic I saw a young woman, a volunteer worker in a secretarial capacity. She had a pronounced sensitization to vertebrate fish, affecting the mucosa of the respiratory tract, with gastro-intestinal distress and generalized urticaria lasting for about five hours, and returning to normal at the end of 24 hours, but leaving the patient completely exhausted. As I had no fish extracts at that time, I hastened to prepare some, and after obtaining characteristic skin-reactions without any constitutional disturbance, was surprised to learn that the testing had conferred such a degree of immunity that for six weeks she was able to eat all the fish to which she had been proved sensitive, without any reaction. But after about six weeks all the manifestations were renewed, and other physicians agreed that the girl was a "neurasthenic." I am still convinced however, that the skin tests told the truth, that my extracts were efficient, and that the fact that abstinence from the offending fish protected her from the symptoms, demonstrated the efficiency of the method.

C. OPPOSITION BY REFERRING PHYSICIAN.

1. I found that a patient referred to me by a gastroenterologist was sensitive to banana. On reading this in my report, he found it ridiculous that "a simple thing like banana could hurt anybody," so did not impress upon the patient the necessity of following the diet exactly, and another failure was chalked up against me. When I informed another physician that his 50 year old sister was sensitive to goose, he retorted that as she had never in her life eaten goose, it was impossible for her to be sensitive to it. Because he was so ignorant of the mechanism of allergy, he could not understand that it exists even when certain exciting stimulants may never have been encountered. A striking illustration of this is the reaction to albumin—nausea, vomiting, asthma, or even collapse—which a child may undergo when given its first egg.

Such children are often referred to me by pediatricians, not infrequently *after* they have been tested by other allergists and pronounced "negative." One mother of a 7 year old girl, for whom she had sought relief (unsuccessfully) from chronic "colds," asthma, and bronchitis, by visits to pediatricians, was so infuriated at their failures to discover the cause of her child's reactions that I had difficulty in dissuading her from returning to accuse them. Another little girl was in a similar condition, and also presented so severe a gingivitis that the dentist had to remove the bands which he had placed on her teeth. She had fallen so far behind in her school work that a private tutor had to be employed. Properly tested and placed on the indicated diet, she not only got rid of all allergic mani-

festations but her mental state likewise "cleared," so that she received "A" marks in all her studies.

A woman whom I tested, after several other practitioners had found her "negative," reacted to cat-hair as well as various food-proteins. One allergist said he had a "hunch" she had an endocrine disturbance, but admitted the "hunch" had no scientific basis. But the woman herself instantly recognized the relation of her symptoms to her visits to a friend who had a cat. By avoiding the cat, as well as the forbidden foods, she recovered perfectly from a severe disfiguring eczema.

If skin tests were made a part of the routine "physical checkup" given where diagnosis is in doubt, or there are no definite complaints but only a feeling of being physically "below par," I am certain many unsuspected sensitizations would come to light. Such a patient came to me in a roundabout way. His dentist, whom I had successfully treated for angina pectoris and arterio-sclerosis, so impressed this man with the importance of detecting and treating allergy, that he urged his *fiancée* to consult me for her weakness, exhaustion, and low blood pressure. She agreed to do this on condition that *he* would also undergo the tests and receive treatment for what she considered overweight.

The young lady was tested and treated with excellent results, but when the man's turn came, he confided to me that he was merely keeping faith with his *fiancée*, there was "nothing wrong" with him. None the less I took the history and made the tests exactly as for a very ill patient. The systolic pressure was 100, the diastolic 70. The only complaint was "some mucus comes into my throat." A diet in accordance with the readings of the skin tests was ordered. In two weeks this patient returned with a systolic pressure of 120, there was no more mucus in the throat, and a previously experienced sense of bloating and distention in the stomach, which he had "thought was natural," had entirely left him. Such results prove the efficiency of the skin tests, and the results which may be obtained by proper diet regulation. They also

illustrate how much the allergist must depend upon the faithfulness and enthusiasm of his patient.

Frequently, in medical periodicals, articles appear reporting the failure of self-styled "allergists" to obtain skin reactions to proteins upon patients suffering from eczema, urticaria and psoriasis. They also claim a large percentage of negative results in vaso-motor rhinitis, or even in asthma. A recently published editorial, based upon such reports will undoubtedly do much to prejudice medical men who have no special knowledge concerning allergy, against the use of skin tests. It is my contention that such failures are due entirely to ignorance and inexperience on the part of the examiner, failure of the patient to cooperate, or—most frequently—to both. I am confident that if the skin tests are properly made with reliable test-substances, and *properly interpreted*, if the patient's dietary regimen and environmental regulations are precisely laid out and *strictly followed*, the detection and successful treatment of allergy is absolutely assured.

SUMMARY

1. Allergy can only be detected and treated properly by those who have had careful training and long experience in this work; who are skilled in interpreting the varied reactions given by different types of skin, and who have the patience to give each case the benefit of all possible sensitizing proteins (I regularly use 240 different test substances).

2. Lack of cooperation on the patient's part, in cases where tests are correctly made and interpreted, is the cause of failure in treatment. Referring physicians often modify or nullify the allergist's directions when patients are returned to them; outside physicians frequently condemn all testing and dieting for protein sensitization, thus undermining the general public's confidence.

3. Allergy is an important subdivision of internal medicine, and its detection and treatment should receive far wider consideration and practice. The results obtained by skilled allergists with cooperative patients are highly gratifying.

The Nutritional Basis of Nervous Disorders in Children

by

I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D.

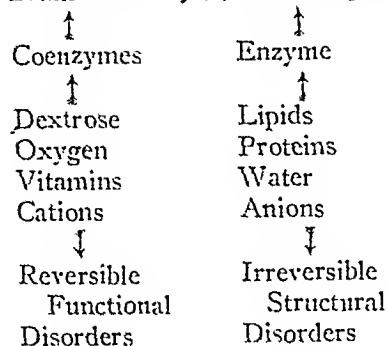
NEW YORK, N. Y.

THE brain controls directly, by nerve impulse or indirectly through the blood stream, the activity of all other tissues of the body. Its development sets the pace for the development of all other tissues as the first in embryogenic formation; its work entails perception, memory, concentration, judgment and reason; its function involves the regulation of the involuntary functions of every part of the body. The mental energy essential for the performance of brain and body

function is a product of two distinct factors, i.e., the quantity or capacity factor and strength or intensity factor. This formula is analogous to that applicable to all other forms of energy compounded of the same two factors. Since the infant's nervous system is far from being complete at birth, we are concerned with both changing capacity and intensity factors throughout maturation. The structural or capacity factor requires all nutrients essential for the development of the body as a whole, especially proteins, liquids and

minerals through enzyme activity. The functional or intensity factor on the other hand requires at least four components—dextrose, oxygen, vitamins and minerals through coenzyme activity. Alteration in brain structure leads to mental deficiency, while alteration in brain function leads to aberrations in behavior; the one involves irreversible anatomical lesions while the other to reversible biochemical lesions.

$$\text{Mental Energy} = \text{Brain Intensity} \times \text{Brain Capacity}$$



MULTIPLE NUTRIENT DEFICIENCY

The nutrition of the brain is best maintained on an adequate regimen until we know more about the brain metabolism of each nutrient. Protein nutrition has not been sufficiently studied although all amino acids except cystine have been isolated from the brain tissue. Allergenic protein, however, may produce reactions in the cranial cavity simulating brain tumor, cerebral anemia, psychosis and neurologic manifestations as a result of cyclic vomiting, Meniere's syndrome, migraine or epilepsy. Carbohydrate nutrition is limited to dextrose as the sole source of energy with little carbohydrate reserve in the brain. Lipid nutrition is active but limited to brain structure since no energy is formed from oxidation of fat and no fat is stored

maintaining at the head of the class. Apparently, provision of the components essential for brain energy in a mind of exceptional brain capacity does not interfere with the calibre of the mental work. The role of some essential nutrients has been evaluated in the mental activity of experimental animals but the applicability of this knowledge to children is a moot question. Since multiple nutritional deficiency predominates, the pertinent problem is to determine the effect of malnutrition on retarding mental function. Despite the difficulty of evaluating the nutritional status of children at various ages and the task of excluding underlying diseases affecting mental growth, we have, nevertheless, been able to study the effects of nutritional improvement on child mentality in 182 children from 2 to 9 years of age, half institutionalized and half out-patients.

Group I included 41 retarded and 50 average children malnourished at the time of the first mental test and well nourished at the time of the second test. Group II included 41 retarded and 50 average children, well nourished at the time of the first test and still well nourished at the time of the second test. Each group was equated for chronological age, I. Q. and interval between Kuhlmann-Binet or Stanford-Binet tests. The data in the tables reveal an average rise of 10 points for retarded and 18 points for healthy children of Group I in contrast with an average zero change for the retarded and a -0.9 change for the healthy in Group II. The greater variability shown by higher standard deviation of I. Q. in Group I in comparison with Group II is probably due to the initial variations in nutrient deficiency and individual responses to nutritional therapy. The significance of this difference in I. Q. change in favor of the malnourished group is 2.43, indicating that chances are 99.2 in 100 that the difference is greater than zero.

TABLE I
Effect of Nutrition on Mentality

	Malnourished Groups			
	41 Retarded		50 Normal	
	Range	Average	Range	Average
Age	2 8 years	3 years 10 months	2 10 years	4 years 8 months
I. Q.	20 90	45	95-145	110
Interval	1-7 years	3½ years	1-3½ years	2 years
I. Q. Change	-8 to +44	+10	-12 to +55	+18
	Well-Nourished Groups			
	41 Retarded		50 Normal	
	Range	Average	Range	Average
Age	2 8 years	4 years 10 months	2 10 years	5 years
I. Q.	20 90	52	95-140	110
Interval	1 8 years	3½ years	1-3 years	2 years
I. Q. Change	-20 to +11	-0 3	-25 to +20	-0 9

beyond growth requirements. Most of the vitamins have been found in brain tissue but only the specific role of water-soluble vitamins is thus far established.

Experimental and clinical data have revealed that any nutrient deficiency decreases mental function but few data are available on the role of nutrition in improving mental potential of children. The old dictum correlating a healthy body with a healthy mind does not necessarily hold, for some malnourished children fail in their school work, while others show a strong desire for constant mental activity and succeed in re-

There is a significant correlation between the age at the time of the first test and I. Q. rise. A correlation of -0.56 is a clear indication that the younger the malnourished child when nutritional therapy is instituted, the greater the chance of improvement in mental function. Indeed, the sharp decline in average I. Q. rise for the malnourished group after the age of 4 years suggests that irreparable damage is to be expected in older children. Flexibility of I. Q. change during the first four years of life bespeaks of reversibility in mental development, while relative constancy

in I. Q. change in older children indicates irreversibility in mental development following prolonged malnutrition. The slightly positive correlation between the length of interval and I. Q. rise in the malnourished

TABLE II

I. Q. Change/Age in Mentally Deficient Group

Age	Malnourished		Well Nourished		Difference
	No. of Cases	Average I. Q. Change	No. of Cases	Average I. Q. Change	
2	11	-13	5	-2.4	-10.6
3	15	-14.4	7	-2.8	-11.2
4	8	-5.3	10	-1.8	-7.1
5	0		8	-1.6	
6	5	-1.6	9	-0.7	-2.3
7	2	-0.5	2	-1.0	-0.5

I. Q. Change/Interval in Mentally Deficient Group

Interval	No. of Cases	Average I. Q. Change	Range
0 mos. to 11 mos.	11	-5.6	4 to -20
12 mos. to 18 mos.	12	-6.8	0 to -26
19 mos. to 25 mos.	7	-10.7	2 to -28
26 mos. to 32 mos.	6	-11.3	0 to -23
33 mos. to 5 yrs	5	-0.6	10 to -9

group as compared with the zero correlation of the well nourished group suggests that as long as two years may be necessary to bring about the average gain in I. Q. following nutritional therapy.

A striking feature of the mentally healthy malnourished group was spontaneous alleviation of nervous symptoms with improvement in nutrition. The children became more interested, attentive, responsive and showed greater ability to concentrate upon their school tasks. Even those who were mentally alert, precocious and overambitious despite under nutrition showed greater stability in behavior and greater purposiveness in activity. Many nervous manifestations such as tics, nail biting, fidgeting, fretfulness, sleeplessness, bed wetting and night terrors diminished but did not clear during the course of these observations.

DEXTROSE DEFICIENCY

The brain requires dextrose continuously for energy since it can oxidize no other sugar. Reserve glycogen is insignificant and available cerebroside and galactose cannot burn in the brain. Even in total diabetes the brain utilizes dextrose from the circulation when the rest of the body derives most of its energy from oxidation of fat. Most causes of hypoglycemia are due to disturbances of the nervous system, to diseases of the liver and to hyperinsulinism, organic and functional. True hyperinsulinism is a rare chronic disease of the pancreas characterized by symptoms of hypoglycemia after long periods without food, low fasting blood sugar, prompt relief by ingestion of food, flat dextrose tolerance curve and excessive rate of dextrose removal from the circulation. Relative hyper-

insulinism occurs in healthy newborns as a result of birth shock; in infants born of mothers with uncontrolled diabetes; in diseases of the liver, especially infections, poisoning and von Gierke's disease; in dis-

TABLE III

I. Q. Changes in Mentally Deficient Children

	Malnourished Group		
	Range	Average	Standard Deviation
Age	2 yrs 1 mo to 7 yrs 10 mos.	3 yrs. 10 mos	1 yr 5 mos.
I. Q.	22 to 82	45	16
Interval	8 mos. to 7 yrs 0 mos	3 yrs 7 mos	1 yr 6 mos
I. Q. Change	-8 to +44	-10	12
	Well-Nourished Group		
	Range	Average	Standard Deviation
Age	3 yrs. 7 mos to 7 yrs 7 mos.	4 yrs. 10 mos	1 yr. 7 mos
I. Q.	22 to 89	52	19
Interval	8 mos. to 8 yrs. 9 mos.	3 yrs. 4 mos	2 yrs. 1 mo
I. Q. Change	-20 to +11	-0.3	6

Intercorrelation* by the Pearson-Product-Moments Method

Age vs. IQ	-0.16 ± .08 P.L.	-0.03 ± .106 P.L.
IQ vs. IQ rise	-0.149 ± .10	-0.25 ± .106
Interval vs. Age	-0.028 ± .10	-0.10 ± .102
Interval vs. IQ rise	-0.221 ± .102	-0.34 ± .106
Age vs. IQ	-0.23 ± .102	-0.07 ± .106

eases of the endocrine glands, especially Addison's disease, Simmond's disease and hypothyroidism; in diseases of the nervous system, especially anorexia nervosa, hypertonicity, vagotonia, neurosis, asthenia, psychosis; paralysis and epilepsy.

Whatever the cause of hypoglycemia the symptoms are referable to the central nervous system. They vary from mild degrees of irritation, fatigue, or hunger to extreme weakness, unconsciousness and convulsions. Flushing, sweating, pallor and cyanosis may occur even in the newborn. On the other hand, extremely low blood sugar values may fail to induce these characteristic manifestations in very young infants because of inadequate development of the central nervous system. The threshold, therefore, of hypoglycemia is lower in children than in adults. Prodromal symptoms consist of nervousness, sleeplessness, pallor, salivation, decrease in cortical activity and slowing of mental function. Neural manifestations begin with restlessness, diplopia, facial twitching and proceed to convulsions, hemiplegia, aphasia and sensory disturbances. Psychic features are pronounced ranging from anxiety, depression, lack of concentration, thick speech, facial grimacing, emotional imbalance and hysteria to eventual loss of consciousness.

A group of non-diabetic children have been observed with various nervous disturbances referable to hypoglycemic states. The only case of true hyperinsulinism was due to physical hyperactivity of the pancreas brought about by excessive carbohydrate intake. The child was maintained on a predominantly high sugar

and starch regimen with consequent obesity. An abrupt change to an adequate regimen precipitated a hypoglycemic attack. Other cases showed relative hyperinsulinism due to various causes but the symptoms of hypoglycemia were not closely correlated with the level of blood sugar. In general, the first stage was characterized by fatigue, lassitude and reluctance to physical or mental effort. The child becomes pale, drawn and tearful. The second stage attributed to compensatory adienalin secretion as characterized by clammy perspiration, palpitation of the heart, tremor of the hands and sensations of thirst and subjective

prompt relief of serious degrees of low blood sugar levels and prevention of acute attacks. The first is accomplished by oral or parenteral administration of dextrose solutions and the second by dietary regulation. Epinephrin (1:1000) several minims may revive a child sufficiently to take dextrose by mouth. Otherwise, rectal or intravenous dextrose solutions are emergent. Thereafter three meals a day are reinforced with small feedings of easily assimilable carbohydrates between meals and at bedtime. This will obviate the indiscriminate nibbling by nervous children in order to overcome the effects of low blood

TABLE IV
Anoxia in Nervous Disorders

Age	Type	Cause	Symptoms
W K, 5 years	Anoxic (low oxygen saturation of heb. arterial blood)	Congenital heart disease	Weakness, faintness, headache, dizziness, syncope, loss of self control, excitement, cyanosis
C J., 10 years	Anoxic (mechanical interference with oxygen absorption)	Bronchial asthma	Depression, apathy, drowsiness, intellect and senses dulled, dyspnea, neurasthenia, cyanosis
B F, 12 years	Anemic (oxygen content by low hgb)	Microcytic hypochromic anemia	Fatigue, irritability, forgetfulness, frustration, sleeplessness, neurasthenia
A F, 14 years	Stagnant (oxygen supply inefficient)	Myocardial failure	Fatigability, dyspnea, headache, dizziness, fainting attacks, incoordination in gait, loss leg power, nausea, vomiting, anorexia

symptoms of fear and panic. The third stage was characterized by dullness, confusion or indistinct speech, belligerency, tantrums, anger and rage. The final stage of coma was not observed in these non-diabetic children, except in a case of recurrent vomiting complicated by alkalosis. One of these children is representative of many who are considered mentally retarded because of repeated school failures. Actually they showed normal I. Q. levels despite drowsiness, fatigability, poor understanding, lack of concentration and forgetfulness. Unfortunately, detection of hypo-

sugar. In many cases such a regimen may increase the hypoglycemic attacks since large amounts of carbohydrate stimulate the insulogenic mechanism and thus produce a vicious cycle. Consequently, the high protein, moderate fat and relatively medium carbohydrate formula is more advantageous. The evenness of the rate with which carbohydrate is liberated from protein, the slowness of fat absorption makes this the diet of choice. To assure more complete utilization of dextrose in muscle metabolism adequate amounts of thiamin are essential.

TABLE V
Hypoglycemia in Nervous Disorders

Age	Type	Cause	Symptoms
C D, 4 years	True hyperinsulinism (physiologic hyperactivity)	Abrupt change from high carbohydrate diet	Fatigued, dull, weepy, fearful, irritable, faint
J B, 5 years	Relative hyperinsulinism (endocrine imbalance)	Familial; follows digestive or infectious diseases	Sudden rage, screaming, kicking, facial twitching, thick speech, convulsion
F W, 7 years	Relative hyperinsulinism (recurrent vomiting)	Focal infection—sinusitis	Languor, dullness, anorexia, vomiting, irritability, stupor
M B, 8 years	Relative hyperinsulinism (recurrent diarrhea)	Food allergy—milk, wheat, egg	Anorexia, lassitude, diminished effort, poor school work, fear, day dreaming
G N, 9 years	Relative hyperinsulinism (starvation)	School vomiting—psychogenic	Worried, anxious, excitable, tense, panicky, fearful, vomiting, perverse, fidgety
C F., 10 years	Relative hyperinsulinism (starvation)	Undernutrition—discordant home	School failure, drowsiness, fatigability, despondent, weepy, forgetful, dreamy

glycemia was difficult because the conditions responsible for these states were not always producible under routinized scrutiny. With elimination of the underlying factors responsible for nutritional failure, the hypoglycemic state was corrected with corresponding improvement in mental function.

Treatment of true hyperinsulinism is surgical but that of relative hyperinsulinism is directed toward

OXYGEN DEFICIENCY

The brain requires a continuous supply of oxygen from the circulation. Oxygen reserve in the capillary bed suffices for 10 seconds and the survival time of the nervous tissue without oxygen is limited to 20 seconds. The brain consumes 10% of the oxygen intake of the body and the cortex ten times as much as the white matter. This is an enormous amount of

oxygen utilized by the gray matter if one recalls that there is but one cubic inch of the substance embodying the seat of conscious mental activity. The effects of low oxygen tension are equivalent to those of hypoglycemia for both are involved in the energy yielding reaction. There is progressive loss of reasoning, judgment and insight. When anoxia is rapid, loss of consciousness may occur without warning. If anoxia develops gradually the intellect and the senses become dulled without the child being aware of what has happened. Headache, depression, apathy and drowsiness or excitement and loss of self control may develop. Understanding is impaired more than sensation, although the senses wane, hearing being retained the longest. Incoordination in walking is followed by loss of power in the legs and paralysis of the arms.

Three types of anoxia occur in children: (1) the anoxic type where the oxygen tension in the arterial blood is lower than normal develops in congenital heart disease, in mechanical interference with oxygen absorption, in pulmonary disorders and in high altitudes; (2) anemic anoxia where the quantity of hemoglobin is diminished occurs in all forms of anemia, methemoglobinemia, sulfhemoglobinemia and carbon monoxide poisoning; (3) stagnant anoxia due to circulation insufficiency occurs in decompensated heart disease, shock and vasospastic phenomena.

THIAMIN DEFICIENCY

Thiamin pyrophosphate is essential for the utilization of pyruvic acid, the intermediate degradation product of carbohydrate metabolism within the cells. In thiamin deficiency, therefore, pyruvic acid accumulates in various tissues and body fluids just as dextrose accumulates in insulin deficiency. Pyruvemia, i.e. levels exceeding 1 mgm.% normal is thus the chemical index of thiamin deficiency. It concerns the brain more than any other tissues because it depends predominantly upon combustion of carbohydrate. The rise in pyruvic acid levels of the blood decreases dextrose utilization by the brain, normally 15 mgm.%, with consequent decrease in oxygen utilization. The resulting depression in cerebral metabolism explains

mental changes observed in children with thiamin deficiency. It may develop in nursing infants as a result of a deficient maternal dietary; in infants and young children as a result of a high carbohydrate regimen; and in older children with organic disease affecting intake, assimilation or utilization of essential nutrients, especially during periods of rapid growth.

Neurasthenia is the functional disorder first observed in thiamin deficiency. It is manifested by fatigability, anxiety, irritability, forgetfulness, headaches, impaired judgment, bodily complaints, hypersensitivity, frustration and sleeplessness. The child's personality is characterized by a minus in view of his inability to do things. If no irreversible basis is found for this behavior an adequate dietary reinforced with thiamin improves, even if it does not cure the condition. I have been unable to differentiate this syndrome from psychogenic disorders nor to observe any striking benefit from thiamin therapy *per se*.

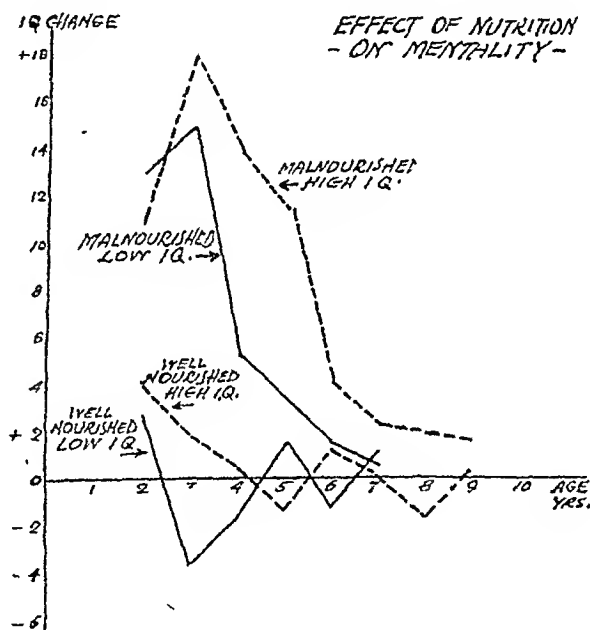


TABLE VI
Thiamin in Polynuropathy

Age	Type	Features	Response
I. W., 2½ yrs	Acro-dynia (infection?)	Upper respiratory infection, cutaneous lesions, muscular hypotonia, loss tendon reflexes	B ₁ 2 weeks ± B ₁ 2 weeks ± Duration 9 weeks
B. J., 3 yrs.	Lead (paint)	Mental deficiency, colic, neuritis, encephalopathy, anemia (stippling), epiphyseal density	B ₁ 2 weeks + C 3 weeks ++ Hemolytic anemia
B. L., 5 yrs.	Arsenic (rat poison)	Digestive disturbances, parasthesia extremities, facial edema	B ₁ 4 weeks +++
A. G., 6 yrs	Infective (Guillain-Barre)	Upper respiratory infection, muscular weakness, facial nerve paralysis	B ₁ 6 weeks + B ₁ 2 weeks ±
W. H., 8 yrs.	Uveoparotid (infection)	Digestive disorders, bilateral parotitis, bilateral facial palsy	B ₁ 8 weeks ++
I. E., 9 yrs.	Porphyria (sulfonamide)	Digestive disorder, convulsions, hyperesthesia, polyneuritis	B ₁ 1 week +++

Neuropathy, induced by infectious, chemical cachectic, digestive or metabolic disorders represent anatomical lesions or nerve degeneration due to thiamin deficiency. It is invariably associated with decreased gastric HCl, anorexia, vomiting, diarrhea and other digestive disorders thus impairing utilization of food. The clinical picture is often obscured by multiple vitamin deficiency for absence of A, B₂, C and D may also lead to degeneration of the spinal cord, roots and nerves. Conversely, their presence may prevent degeneration caused by poisons which affect the nervous system. Early recognition of thiamin deficiency neuropathy is based on the presence of plantar pain and calf muscle tenderness. If, in addition the ankle jerks become absent the diagnosis is established. As the deficiency progresses the knee jerks disappear, impairment of position sensation in the toes develops and

vibratory sensation up to the pelvis wanes. In extreme cases the upper extremities may become involved so that the biceps and triceps reflexes disappear and glove pain and loss of finger dexterity develops. As a rule these manifestations are bilateral and symmetrical in true thiamin deficiency.

I have observed occasional cases of polyneuropathy of various etiology and have attempted to evaluate the role of thiamin in each case. As this type of disease tends to spontaneous recovery it is difficult to estimate the value of any method of treatment once the underlying cause is removed. Nevertheless, the dietary history in cases of acrodynia, lead poisoning and uveo-parotid neuropathy showed evidence of multiple nutrient deficiency. Since digestive disorders were present in all, interfering with absorption and utilization, thiamin or pyridoxin were administered in massive doses according to individual indications, although the evidence in each case is not very striking for a deficiency disease. Thiamin, nevertheless, induced a more favorable response than anticipated in such degenerative processes.

NICOTINIC ACID DEFICIENCY

Niacin is present in the molecule of two coenzymes involved in intercellular oxidation. The coenzymes concentration in the red blood cells is thus an index of the adequacy of nicotinic acid. Low values for enzyme concentration occur in children with infectious disease, diabetes, leukemia and other conditions associated with decreased supply, inadequate assimilation, increased demand or increased loss. The resulting reduction in normal cellular respiration is reflected in functional disturbance in various organs of the body, especially those weakened by hereditary predisposition. A marked lowering of the coenzymes in the blood, brain and renal cortex may be incompatible with life but moderate lowering leads to anatomical lesions characteristic of pellagra or nutritional encephalopathy. Prodromal symptoms are ill-defined before the diagnostic triad of diarrhea, dermatitis and dementia develops, especially in pellagrous families. The maternal diet during pregnancy and lactation is inadequate, the breast milk defective and the infant maintained on a high carbohydrate regimen. He becomes irritable, frightened, apprehensive, listless, apathetic, tired and sleepless. These manifestations wax and wane, increasing in severity until anatomical lesions induce full blown features of the disease. Such a child becomes retarded mentally until specific therapy is instituted. If the condition has progressed beyond the first growth cycle, there may be loss of memory, confusion and confabulation in one type or excitement, depression, mania or delirium in another type. Treat-

ment instituted early reverses the biochemical and some of the anatomical lesions but delayed therapy leaves residual physical and memory defects.

PYRIDOXIN DEFICIENCY

Asthenia accompanying other deficiencies of the vitamin B complex is due to pyridoxin deficiency. It is characterized by weakness, nervousness, irritability, abdominal pain and difficulty in walking and relieved dramatically by administration of pyridoxin but unrelieved by thiamin, nicotinic acid or riboflavin. On this account pyridoxin has been advanced for the post-encephalitic syndrome, parkinsonism, in which ataxia and lethargy have been occasionally relieved.

POTASSIUM DEFICIENCY

Familial periodic paralysis is characterized by recurrent attacks of flaccid paralysis, probably due to potassium deficiency. The deep reflexes disappear and the muscles become irresponsive to electric stimulation. Various conditions precipitate an attack consisting of exposure to cold, fatigue, worry, excitement or dietary indiscretion. The diminution in serum potassium during an attack may be spontaneous or induced by dextrose, insulin, thyroid, epinephrin or ephedrine. The underlying chemical defect is in the central nervous system and in the muscles. Urinary potassium excretion decreases markedly during an attack, hence potassium is not lost from the body but distributed through tissue fluids and cells.

CALCIUM DEFICIENCY

Tetany in infants results from calcium deficiency, rickets, celiac disease, tropical sprue, parathyroid deficiency, prolonged vomiting, overventilation of the lungs or administration of alkali. It is characterized by carpopedal spasm, laryngismus stridulus and convulsions due to diminution in the calcium ion concentration of the blood. Parathyroid tetany due to actual insufficiency is rare in infancy although absence of parathyroid or atrophic changes may occur. Postoperative tetany is occasionally seen after operation with or without injury to the parathyroid glands. Gastric tetany follows loss of acid gastric secretion by vomiting alkali and thus decreasing the calcium ion concentration to critical levels. Hyperventilation tetany is due to loss of carbonic acid through the lungs resulting in alkalosis and consequent reduction in ionized calcium. Chemical tetany may be induced by administration of salts which combine with calcium, especially carbonates, phosphates and citrates. Nephritic tetany is brought about by retention of inorganic phosphates which depress serum calcium to critical levels. Celiac tetany is due to reduction of serum calcium as a result of failure to absorb adequate amounts of vitamin D.

Book Reviews

Practice of Medicine: by Jonathan C. Meakins, M.D., L.L.D., Fourth Edition, pp. 1444, St. Louis, The C. V. Mosby Company, 1944, \$10.00.

This "practice" continues to be one of the best balanced of those currently popular with the medical profession, partly because of its practical basis on physiological principles, but also because of the author's wide grasp of a field which, as he states, is becoming discouraging because of its vastness. In spite of this, it would be unfortunate were "practices" to cease in favor of special monographs, provided such "practices" can continue to give the reader in condensed form so general a description of disease, as the present volume affords. The section on gastro-enterology is particularly attractive and profusely illustrated with informative X-ray reproductions. It is regretted that no more than a paragraph is devoted to gastroscopy, but otherwise it would be difficult to find a more capable treatment of digestive diseases. The cardiovascular section is notable for its cardiographic presentation of the arrhythmias. The entire book contains a wealth of beautiful illustrations. It can be most highly recommended to all practitioners.

Diseases of the Digestive System: Edited by Sidney A. Portis, M.D., 2nd Edition, pp. 932, 182 engravings, Philadelphia, Lea & Febiger, \$11.00.

The list of contributors to this improved second edition includes a sizeable fraction of the men who are most outstanding in American Gastro-enterology, and each has happily been asked to write about that phase of the subject with which he has been most closely associated in his own work. One result is a freshness of touch and a disregard of unsupported tradition. Gastroscopy is suitably covered. What is called "psychosomatic medicine" receives attention. Franz Alexander deals with psychosomatic disturbances of the gastro-intestinal tract from the standpoint of an analyst or "depth psychologist" dealing with such conditions as anorexia nervosa, cardiospasm, gastric neurosis, diarrhea and constipation. The editor is to be congratulated upon introducing these comparatively new concepts into a textbook and Alexander's contribution is stimulating. Many hard-headed gastro-enterologists, however, still are opposed to too general an acceptance of the diagnostic and therapeutic implica-

tions of the psychoanalysts. Portis himself who is known to keep an open mind on this aspect of disease, reports his own work on the effects of psychic fatigue on the body's energy system, particularly the metabolism of carbohydrates. The section on gastro-intestinal allergy emphasizes the potential scope of this subject,—one which is neglected simply because most doctors have neither the time nor training to put it into practice. Endocrine influence on digestion, the gastro-intestinal manifestations of arthritis, the tract in pellagra, are but a few of the separate chapters, whose inclusion demonstrates the breadth of treatment which the editor conceived for this book. Hurst, who sends a chapter from England on mucous colitis, shows himself to be largely nihilist in treatment, confessing that a course in psychotherapy often does more good than local treatment. From the literary angle the book maintains a high standard: all authors state the facts clearly and acceptably, the one most closely approaching "stylism" being Hurst. We can recommend this volume for its comprehensive grasp, specialistic treatment of the various subjects, and its "modern" tone.

Gastro-intestinal Tract. A handbook of Roentgen Diagnosis, by Fred Jenner Hodges, M.D., Chicago, The Year Book Publishers, Inc., \$5.50, pp. 320.

Unique, fascinating and permanently valuable, this book displays on every right-hand page X-ray photographs of one or more organic lesions of the gastro-intestinal tract, while on every left-hand page opposite is a succinct resume of the case, a description of the illustration, and, not least important, one or two valuable hints on some phase of X-ray technique. The illustrations are clear and superbly reproduced. The text affords a veritable storehouse of X-ray and clinical wisdom, developed over a period of many years' experience. Every roentgenologist ought to own the book, but it is imperative for the internist, who, challenging Dr. Hodges' better judgment, insists on doing his own screening and film interpretation. The esophagus, stomach, duodenum, small bowel, biliary tract, colon and the abdomen generally all receive exhaustive consideration. Approximately 150 pages of illustrations constitute a veritable reference album, and must have made the publication expensive. What this book teaches about peptic ulcer alone is worth \$5.50.

Editorial

THE SPECIAL AND THE GENERAL

THE recent Presidential address of Anthony Bassler, M.D., before the Ninth Annual Convention of the National Gastroenterological Association in New York, is valuable for several reasons. It contains a useful historical review of the work of gastroenterologists from the beginning up to current days in the United States. Bassler feels that progress has stalled today, perhaps because of controversy and prejudice in the organizational field. He is strongly of the opinion that gastroenterology cannot profitably be divorced from internal medicine, and eulogizes the policy of the American Board of Internal Medicine which requires a candidate to be qualified in internal medicine before he can be classified in a submedical branch. Bassler does not feel that membership in any gastroenterological society is, *per se*, evidence of proficiency in this field.

Perhaps Dr. Bassler's chief contribution in this address is his conception of the abdominal specialist,—one who, as a result of patient study, is able to detect which one of several hundred possible diseases is present in the particular abdomen which he is examining. Such accomplishment presents the insuperable difficulties instinct in the shortness of life and of professional experience. Just as it would be desirable to have a "head specialist" who could skilfully know what is the matter in a patient's head, without reference to neurologists, neurological surgeons, E.E.N.T. men, nutritionists and psychoanalysts, so by enlarging the concept of regional experts, one for the chest and one for the extremities, we would lessen the eventual category of specialists. This is not so much a *reductio ad absurdum* argument as it is a reflection on the profundity of specialistic knowledge.

Dr. Bassler rightly asks for clearer issues in the future—we need pioneer initiative and a better understanding among our organizations if gastroenterological knowledge is to grow. We need less laboratory work and more clinical acumen. Less restricted specialism of thought and more attention to disease outside the gastrointestinal tract, reflecting itself within the tract. Perhaps, even in the largest cities, where only the specialist counts today, the internist (the man who knows quite a lot about everything) may again be able, as he once was able, to make a living in medicine.

Dr. Bassler's address supports the theme of the well-trained general man, which this journal has consistently supported. We think that his address deserves wide consideration. He is not advising deletion of the specialty of gastroenterology, but rather a more liberal education for those who do this work. Dr. Bassler is one of those comparatively few men in gastroenterology who has worked incessantly, intelligently, and intensively amid a tremendous supply of clinical material and has developed a keen instinct for abdominal diagnosis, based on his enviable experience. He has remained versed in the literature of the subject. There are few organizations of importance in gastroenterology in this country or elsewhere which have not felt his influence in some degree. He has remained a kindly man, with a genuine interest in the welfare and the opportunities of aspiring younger men. In addition to his own constant application to clinical study and medical writing, he has always been ready to lend a hand in medical organization work, where it appeared to him important. He has been very closely associated with the New York Gastroenterological Association as a founder and supporter. He has had much to do with the success of the growing National Gastroenterological Association, which now possesses 26 Chapters, some in Central and South America. He is a past president of the International Gastroenterological Association, whose progress has been temporarily halted by the present war.

We agree with Dr. Bassler's message, and with him, we are sensitive to the current demands upon the gastroenterologist, both from a technical and an organizational viewpoint. With him, we stand for more amiable relations among all organizations pertaining to this specialty.

In a recent editorial in the August 1944 issue of Gastroenterology, Thomas A. Brown, M.D., voices practically the same ideas as Bassler. Brown believes that gastroenterology can never be a narrow, restricted specialty and that the gastroenterologist must be a thoroughly competent internist, "in the broader sense of the word, as well as a thoroughly trained student in the digestive sphere." Brown is opposed to too much dependence on instruments and mechanical devices and pleads that each case be individualized. He feels that no strict ritual of diagnostic procedure should be used nor any rigid formula of treatment followed.

Abstracts of Current Literature

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

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	G. KLENNER	B. C. RIGGS	D. A. WOCKER
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*With the Armed Forces.

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CLINICAL MEDICINE STOMACH

EINHORN, MAX: *Is gastric analysis necessary?* (*Med. Rec.*, v. 157, p. 89, Feb., 1944).

The author presents a brief history of the progress made in gastroenterology and points out the necessity of knowing the state of acidity of the stomach in order to administer further treatment and to make diagnosis. For instance, in cases of hypertrophy, there is usually hyperchlorhydria; in cases of atrophy, hypochlorhydria.

The author believes that gastric analysis is useful and states that many conditions of the stomach and frequently of the intestine may be ameliorated by simple remedies based on the data gained therefrom.—G. Klenner.

BOWEL

DINSMORE, R. S. and ANCORA, V. C.: *Reticulum cell sarcoma of jejunum.* (*Cleveland Clin. Quart.*, v. 11, p. 77, July, 1944).

The case is reported of a 58 year old woman with a reticulum cell sarcoma (lymphosarcoma) of the jejunum. The onset was insidious and the symptoms presented were those of obstruction. At operation the tumor was revealed as a mass involving the midportion of the jejunum. Resection of the involved area and side to side anastomosis were done. Recovery was uneventful.—D. A. Wocker.

TAKER, D. N.: *Hemorrhoids: surgical versus injection treatment.* (*Am. J. Surg.*, v. 65, p. 88, July, 1944).

Assuming that other pathological conditions have been ruled out and the diagnosis of hemorrhoids conclusively established, treatment will depend on the type of hemorrhoids found. Three types are distinguished—internal, external, and mixed externo-internal hemorrhoids and skin tags. The varicosities of the superior hemorrhoidal vein branches which constitute the internal type are covered by mucous membrane. The first symptom is bleeding, later enlargement and protrusion on bowel movement. Pain is present only when the hemorrhoids are thrombosed or strangulated and accompanied by edema of the anal skin. These hemorrhoids respond well to injection treatment. Quinine and urea or mild phenol solutions have given good results.

External hemorrhoids are those situated below the anorectal margin and are varicosities of the inferior

hemorrhoidal veins. They are covered by anal skin. Symptoms are similar to internal hemorrhoids but there is constant protrusion. The only treatment that yields good results is surgery.

The mixed types of hemorrhoids do not lend themselves well to injection treatment and can be relieved successfully by surgery only.—I. M. Theone.

LANDSMAN, A. A.: *Report of a case of fecal impaction.* (*Med. Record*, v. 157, p. 155, March, 1944).

The discussion is concerned with impaction caused by a retained fecal mass. In such cases the mass backs up into the ampulla behind the anal canal. A "ball-bearing valve" is formed which is difficult to remove because it slides up when attempts are made to grasp it. Such a condition often leads to intestinal obstruction.

In the case here presented the mass was removed by fastening several rolled towels to the center of the abdomen by means of adhesive tape and applying pressure above this pad. The operator was then able to steady the mass and break up the impaction by placing 2 fingers in the vagina and hooking them over the upper limit of the mass. The impaction was then removed piecemeal.—I. M. Theone.

WILDER, R. M.: *The non-tropical sprue syndrome: Report of four cases and a case in which intestinal insufficiency was corrected by operation.* (*Proc. Staff Meet. Mayo Clinic*, v. 19, p. 297, June 14, 1944).

Sprue, a type of jejuno-ileal functional insufficiency, is a chronic recurrent non-inflammatory intestinal disorder which results in diminution in absorption of the products of digestion as well as in inadequate absorption of minerals and vitamins. Inadequate absorption of fats is responsible for many of its symptoms, excessive amounts of unsplit fat appearing in the stools which may be frequent, bulky, greasy and foamy, or liquid and brown. Vitamins D, A and K are improperly absorbed, the latter resulting in frequent hemorrhagic diathesis. Calcium metabolism is interfered with and may result in hypocalcemic tetany or even osteoporosis.

Vitamin B complex is grossly deficient evidenced by frequency of cheilosis, angular stomatitis, pellagra-like lesions of the skin and a fiery red tongue.

In active sprue probably all substances including water and gases are absorbed poorly. Sprue is characteristically accompanied by anemia, anacidty (30 to

50 per cent), atony of the intestine, hypomotility and dilatation; excessive amounts of intestinal gas and obliteration of the mucosal folds.

Five cases are reported, one of which had fatty diarrhea and a rather low level of vitamin C in the plasma; the other 4 had marked evidence of nutritional deficiencies. Treatment of all 4 cases of sprue consisted of low fat and residue and rather high protein and carbohydrate diets, calcium where tetany had developed, large daily doses of vitamins A, K, D, C, thiamine chloride and the rest of the vitamin B complex, and intramuscular injections of crude liver extract.—E. R. Feaver.

DECOURCY, J. L.: *The etiology of regional enteritis, the role of inflammatory bands and ileocecal valve incompetence.* (Ohio State Med. J., v. 40, p. 533, June, 1944).

While the condition was originally considered as confined to the terminal ileum, it was later recognized that there was a much wider distribution of the lesion, leading to the term "regional ileitis." It denotes a non-specific inflammatory lesion with a common clinical and pathologic history, involving for the most part the terminal ileum, but to some extent any part of the intestinal tract. The clinico-pathologic description of the acute and chronic forms is presented. Theories concerning its causes have been advanced, but no definite factor has proved convincing. The essayist believes that inflammatory bands produce partial constriction of the lumen with resultant lymph stasis and hyperemia. Partial obstruction due to constriction of the lumen has been invariably found in these cases, but up until now has been considered a result of the inflammatory process. These inflammatory bands or an incompetent ileocecal valve cause partial constriction of the lumen with lymph stasis and hyperemia. An analogy is drawn between appendicitis as a result of obstruction and infection and regional enteritis.—H. N. Metzger.

PANCREAS

FARBER, S.: *The relation of pancreatic achylia to meconium ileus.* (J. Pediat., v. 24, p. 387, April, 1944).

The author states the purpose of this paper was to supply data concerning the relationship of the pancreatic enzyme to the altered physical state of meconium in the patients with meconium ileus.

Eighteen infants were studied post-mortem who presented the clinical picture of high intestinal obstruction, caused by inspissated meconium and revealed in each instance an obstructive lesion in the pancreas, characterized by the inspissation of secretions, dilatation of the ducts, atrophy of the acini, and fibrosis of the pancreas. The meconium was mucilaginous and sticky in consistency, and such physically altered meconium cannot be propelled through the bowel and is responsible for the intestinal obstruction.

Experiments were performed on 13 patients at autopsy or at operation. The use of saline solutions of pancreatin was employed, which varied from 1%

to 10% in strength at a temperature of 37.5 degrees Centigrade. The meconium was then reduced in a short time to semi-fluid or fluid state.

In four cases operated, a 1% solution of pancreatin was employed as a solvent through an enterostomy with the relief of the mechanical blockade of the intestines, but these infants died several days to a few weeks later, due to intercurrent infection. In 2 patients, the author failed to find evidence of tryptic activity.

The obstructive lesion of the pancreas responsible for the meconium ileus may be present not only in the newborn infant, but is also found with regularity in infants under 1 year of age, who had chronic pneumonia and severe nutritional failure, and also in children over 1 year of age who have a type of nutritional failure closely resembling idiopathic celiac disease.

From the results obtained at post-mortem in 18 cases with meconium ileus, an obstructive lesion of the pancreas is important. Caution in prognosis should be exercised. However even when the intestinal obstruction caused by the altered meconium is relieved by the solvent action of the pancreatic extract, possible danger to the later welfare of the patient may still exist because of nutritional consequences of the pancreatic achylia or because the lesion of the pancreas is but one of the many similar lesions involving a number of secreting structures in the body. Inspissated meconium may be found in newborn infants with stenosis of the ileocecal valve or volvulus. In these patients the meconium is not nearly as viscid or mucilaginous in consistency as in patients with pancreatic achylia. In such cases when the partial or complete obstruction of the intestinal tract is relieved the inspissated meconium will offer no great difficulty to removal.

Meconium ileus caused by pancreatic achylia should be differentiated from the clinical much less important inspissated meconium found in patients with partial or complete obstruction to the intestines in the neonatal period.—J. B. Bernstine.

LIVER AND GALLBLADDER

KARLINSKAIA, A. F.: *Cholecystitis in children.* (Pediatrics (Moscow), v. 1, p. 26, 1943).

In 774 autopsies performed in the Rusakov Hospital in Moscow on children from 14 days to 2 years old, 31 cases of undiagnosed cholecystitis were found. Among these were 17 cases of dysentery, 5 cases of toxic dyspepsia, 4 cases of measles, 3 cases of septicemia, 1 case of purulent meningitis and 1 case of diphtheria. Besides these, 1 case of gall bladder hydrops and 2 cases of cholelithiasis were found. The pathological and microscopical findings are described and discussed.—Courtesy Biological Abstracts.

COLP, R.: *Postcholecystectomy syndrome and its treatment.* (Bull. New York Acad. Med., v. 20, p. 203, 1944).

Frequently the removal of the gall bladder does not bring relief to the patient. The persistence of the symptoms postoperatively is referred to as the postcholecystectomy syndrome. Dyskinasia of the sphincter mechanism has been held responsible. Spastic

colon, glandular dyscrasias, psychic disturbances and intrabiliary factors may be the causes of the reflex. Reflex stimulation of the sphincter may lead to stasis of bile, biliary colic and distension of the ducts. The removal of a noncalculous gall bladder in cases with sphincter spasm would therefore bring no relief. Acute pancreatitis and pancreatic edema may recur as a result of the postcholecystectomy biliary reflex and acute attacks of pain in the left upper quadrant may also be due to the reflex. Dilatation of the sphincter by passing increasingly larger sounds thru the bile ducts is advocated but the effects are temporary. Chole-dochoduodenostomy yields permanent results but post-operative complications and mortality are high. Surgical section of the fibres to paralyze the sphincter is suggested—D. A. Wocker.

ULCER

PATTERSON, M.: *Incidence of peptic ulcer.* (*New Orleans Med. J.*, v. 96, p. 551, June, 1944).

According to the author 12 per cent of the American people are subject to peptic ulcer during some period of their lives. Duodenal ulcer is four times as prevalent as gastric ulcer and also occurs earlier in life than does gastric ulcer. The age group 35 to 50 years has the highest number of peptic ulcer cases and it predominates in the male. Hemorrhage and perforation are the most usual complications. The author believes that there may be an endocrine basis and that evidence is still lacking that people subject to nervous strains are the most susceptible. Familial tendency has been shown to exist. In the armed forces more than 30 per cent of the dyspeptics have ulcer, usually duodenal. The ulcer is not precipitated in service men by the conditions of war but rather these conditions are such as to call attention to ulcers already in existence.—Wm. D. Beamer.

FELDMAN, M.: *The wartime duodenal ulcer problem.* (*Radiol.*, v. 42, p. 356, 1944).

Since visibility of an ulcer by X-ray is dependent on the stage of the ulcer development, diagnosis of ulcer by this means may not always be possible. An ulcer may not be shown although it may be present. This is of importance where exclusion from military service is concerned since regulations require a demonstrable anatomic lesion for the diagnosis of ulcer to be accepted. Although the pathological stages have come to be recognized and recorded, the protean stages of the X-ray picture have received little attention. These early roentgen signs are frequently transitory but should nevertheless be looked for. The mucosal changes before the marginal deformities occur should be recognized. The distinct change in the mucosal pattern in duodenal ulcer may be seen in all stages of the ulcer. One of the earliest signs of duodenal ulcer is fragmentation of the barium-filled bulb due to localized edema and spasm. Altered tone, motility, and evidence of spasticity are to be looked for. Thickening of the folds and obliteration of the folds over the ulcer area, distortion of the longitudinal folds and convergence of the folds toward the ulcer are other

changes in mucosal pattern which help the diagnosis—N. M. Short.

MORLOCK, C. G., AND WALTERS, W.: *Peptic ulcer perforating into the anterior abdominal wall.* (*Am. J. Surg.*, v. 65, p. 133, July, 1944).

Though perforation of peptic ulcer into the anterior abdominal wall is rare it does occur, and when it occurs it must be treated surgically. Three cases are reported in this article, all of which started as benign peptic ulcers on the anterior rim of a previous anterior gastrojejunostomy. For this reason the authors believe that the posterior anastomosis should be done in preference to the anterior when surgical treatment of duodenal ulcer is the procedure of choice. Posterior anastomosis allows better function and gives rise to fewer perforations since the adjacent structures are for the most part organs which are more resistant to either perforation or involvement than is the anterior abdominal wall—Glenn Clements.

WILEY, H. M.: *Gastric ulcer, benign or malignant. A review of recent literature.* (*Am. J. Surg.*, v. 65, p. 104, July, 1944).

The relationship of gastric ulcer to carcinoma is problematical. Various sources are quoted to indicate that ulcer may eventuate into cancer, while other reports show that carcinomatous growths ulcerate. The frequency of malignant degeneration of ulcers varies from 1.9% to 71%. Gastritis as a precancerous condition is debatable, since atrophic gastritis is quite common in the aged, and there is only a very slight difference in incidence of gastric atrophy between cancerous and non-cancerous stomachs. However, both ulcer and carcinoma are nearly always associated with gastritis. From a clinical standpoint, the emphasis should be put on determining whether the gastric lesion is benign or malignant. It is often difficult to determine this definitely in the early stages, since a large percentage of carcinomas resemble ulcer in their symptomatology. The duration of symptoms, longer in ulcer (35 months) as compared to cancer (13 months) and the presence or absence of melena helps in making the diagnosis. While X-ray study is the most important diagnostic procedure, a combination of X-ray and gastroscopy will yield the best results. The significance of location and size of the lesion is stressed.—H. N. Metzger.

TIDY, SIR H.: *Death rate from peptic ulcer in Great Britain, 1912-38* (*British Med. J.* No. 4350, p. 677, May 20, 1944).

There are indications that striking changes have occurred during the last 20 years of the period. The number of deaths has been taken separately for the age groups 20-39 years, and for 40 years and over. Between 1912 and 1921, the death rate was practically the same, between 1931 and 1937 it was stationary but at a higher level than in 1921. Between 1921 and 1931, there was an increase of 50%. The increase is found to be almost entirely accounted for by males over 40 years of age. For females over 20, there was

a sharp fall between 1912 and 1921, entirely due to decrease in gastric ulcer between 20 and 39 years. Rates are much lower than for males. The excess of deaths from gastric ulcer over duodenal ulcer is true throughout the period for both sexes, both age groups and all areas of Britain. Between 1912 and 1921, the death rate in gastric ulcer in males rose from 82 to 90; between 1921 and 1928, the rate rose from 92 to 150, an increase of over 60%. In those over 40, the rate increased 90% between 1921 and 1931. For duodenal ulcer, the rate became practically stationary in all age and sex groups after 1930. Death rates for peptic ulcer are highest in London, slightly lower in Scotland, lower for England, and lowest for rural districts of England.—H. N. Metzger.

THERAPEUTICS

ROSENTHAL, A. S.: *Sulphanilamide and diasosulphanilamide in the treatment of dysentery in children.* (*Pediatrics* (Moscow), v. 1, p. 31, 1943).

During the summer of 1940, 60 children with dysentery were treated with sulfonamides. One-fifth gram of the drugs was given per kilogram of weight until improvement was achieved. Afterwards 0.15 gram per kilogram was given for several more days. The results were encouraging. In 8 cases recurrences took place after the drugs were discontinued. No toxic symptoms were seen.—Courtesy Biological Abstracts.

SCADDING, J. G.: *Comparative effects of sulphonamide drugs in mild bacillary dysentery.* (*The Lancet*, No. 6303, 784, June 17, 1944).

The author opens with the statement that it is now generally accepted that sulphonamide drugs have a beneficial effect in bacillary dysentery, although convincing statistical evidence is not yet available. The comparative study reported was made in the Middle East and some of its limitations were (1) control groups of untreated cases could not be included because it was not considered justifiable in a military hospital, whose prime function was to return men to duty as rapidly as possible; and, (2) the fact that at times the supplies of drugs were temporarily limited, with sulphathiazole being unavailable throughout. Also, (3) routine cultures were discontinued early in the study.

1,400 cases were admitted during the observation period. The type of dysentery current at the time was mild and there were no deaths. In treatment the drugs used were given in doses of 3 oz. and the 1 oz. three-hourly for 48 hours. The three suspensions contained in each ounce:

Total dose in 48 hrs.

1. Sulphaguanidine	2.5 grammes	47.5 grammes
2. Sulphapyridine	1.0 grammes	19.0 grammes
3. Sulphanilamide	1.0 grammes	19.0 grammes

Results of treatment were judged by (a) the day on which the stools were first observed to be formed; and, (b) the total duration in the hospital. The cri-

terion for the discharge from the hospital was three successive formed stools free from mucus.

As a result of the observations made two possible conclusions were drawn: (1) in the mild type of dysentery treated, none of the three drugs had any specific effect; or else (2) the drugs in adequate doses are equally beneficial in mild bacillary dysentery. Even so, it was noted that after the limited routine course of sulphaguanidine further treatment was often desirable, and that further treatment was seldom considered necessary after the limited heavy courses of sulphapyridine and sulphanilamide. In several severe cases the impression was gained that improvement resulted from the use of sulphanilamide after sulphaguanidine had produced no favorable results. Concentrated antitoxic serum was accepted as of great value in severe Shiga infections.—G. P. Blundell.

SISK, W. N.: *The modern treatment of pinworm infection.* (*North Carolina Med. J.*, v. 5, p. 52, 1944).

About twenty per cent of the population in the lower income groups are affected by pinworm, also known as the threadworm, seat-worm, *Oxyuris vermicularis* and *Enterobius vermicularis*. Restless sleep, crying during sleep, lack of appetite, nervousness and itching about the rectum are symptoms. Vague epigastric distress and loss in weight are additional evidence of the disease. The red cell count rarely is above 4 million, hemoglobin between 70 and 80 per cent. The only positive method of diagnosis is to obtain swab specimens from the skin around the rectum in the morning. Eradication of the infection is slow. Gentian violet therapy has proved satisfactory but may prove troublesome to the family. Probably superior results are obtained with phenothiazine. One course of treatment will suffice in 60 per cent of the cases. The dosage and routine suggested are given.—G. Klenner.

GEORGE, J. O.: *Treatment of parasites of small intestines with Dover's powder.* (*Northwest Med.*, v. 43, p. 172, June, 1944).

The author's background for this article is based on his practice in Alaska. As the native diet consists largely of fish meat, raw or cooked, reinfection with parasites precluded complete recovery by any therapy. In some 40 individuals receiving Dover's powders (5 grains every 4 hours for 20 doses) for intestinal parasites, most passed large masses of dead worms and were then invariably relieved of their abdominal symptoms. The drug was used successfully on *dibothriocephalus latus* and *ascaris lumbricoides*.—C. Glenn Clements.

MAXFIELD, F. R. JR., McILWAIN, A. J., AND ROBERTSON, J. E.: *Treatment of radiation sickness with vitamin B₆ (Pyridoxine hydrochloride).* (*Radiol.*, v. 41, p. 383, 1943).

The reported successful control of nausea and vomiting in pregnancy with pyridoxine led the authors to attempt treatment of radiation sickness with this vita-

min. More than 50 patients representative of a larger number with radiation sickness were chosen as the subjects. Soon after the sickness developed 25 mg. pyridoxine hydrochloride were given by vein. In the majority of cases the symptoms were gone after the first injection while some patients required additional injections up to the 72nd hour of the X-ray treatments. Appetite returned when the nausea and vomiting were gone and remained unaffected for the duration of the X-ray treatments.—N. M. Short.

SURGERY

MUSHIN, W. W., AND WOOD, H. M.: *Effect of nicotinic acid in postoperative vomiting.* (*Brit. Med. J.*, v. 1, p. 719, May 27, 1944).

Three groups of patients were studied. One group received nicotinic acid following operation, a second group received nicotinic acid both before and after operation, while a third served as a control series. The nicotinic acid treatments did not decrease the incidence of postoperative vomiting as compared with the control group.—F. E. St. George.

MANZER, T. T.: *Surgical treatment of massive gastroduodenal hemorrhage.* (*Northwest Med.*, v. 43, p. 112, April, 1944).

The greatest number of gastrointestinal hemorrhages are due to ulcers of the duodenum or stomach. In patients over 50 years of age, mortality figures range up to 50%, which indicates that medical treatment fails frequently in cases of massive hemorrhages. With this in mind selected cases over fifty years of age were subjected to operation. Of three of these, two were successfully controlled. The third died but the source of hemorrhage was not discovered. The author's plea is that surgery be given a fair trial in cases of massive hemorrhage, and that it be used before bleeding has been so extensive that deteriorating tendencies in the body have begun to take place.—C. Glenn Clements.

STEINBERG, M. E.: *Valvular gastrostomy.* (*Am. J. Surg.*, v. LXV, p. 138, July, 1944).

The disadvantages of the more common types of gastrostomy are pointed out. In Witzel and similar types, the leakage and soiling cannot always be prevented. The authors' method of gastrostomy utilizes a flap from the anterior wall of the stomach. A channel is formed by suturing the seromuscular coat over a rubber tube. The pedicle tube which is formed is then invaginated upon itself, creating a valve-like structure resembling the ileo-cecal valve. This type of gastrostomy was performed in one patient with carcinoma of the esophagus with good functioning results. The length of the pedicle tube appeared to make it unsafe since the invagination might have a tendency to strangulate the blood supply to the terminal portion of the tube. In the newer technique, the length of the finished gastrostomy remains the same as the original one. By separating only the terminal half of the pedicle tube from its continuity with the main body of the stomach, the blood supply is per-

mitted to come from all sides of the main body of the stomach to the distal half of the gastrostomy tube.—H. N. Metzger.

EXPERIMENTAL MEDICINE

SECRETION

BEAMER, W. D., FRIEDMAN, M. H. F., THOMAS, J. E., AND REHFUSS, M. E.: *The effect of gastric and intestinal instillation of bile on gastric secretion.* (*Federation Proc.*, v. 3, p. 3, 1944).

Fresh dog bile or a 5 per cent solution of ox bile when introduced into the stomach resulted in a secretion of gastric juice from the Pavlov pouch after a latent period of 30 to 45 minutes. When introduced into the intestine the bile had no effect on gastric secretion. However, when bile was introduced into the intestine together with a solution of proteoses, then the gastric secretion was greater than that due to proteoses alone.—F. R. Feaver.

PATHOLOGY

PEACOCK, P. R., AND KIRBY, A. H. M.: *Attempts to induce stomach tumors. II. The action of carcinogenic hydrocarbons on stock mice.* (*Cancer Res.*, v. 4, p. 88, 1944).

Stock mice receiving an adequate diet with the addition of either 3, 4-benzpyrene or 20 methylcholantrene in solution in olive oil or cod liver oil developed papillomas of the forestomach, with tendency to malignant evolution. Even a small number of positive results in the experimental induction of tumors of the forestomach of mice must be considered significant in view of the extreme rarity of such tumors in this species. Unlike the diffuse benign gastropapillomatosis associated with dietary deficiencies, papillomas induced with carcinogenic hydrocarbons tend to be localized and invasive, and are not prevented or influenced by the addition of large amounts of vitamin A to the diet. The relative values of stock mice and inbred lines for investigating the competence of tissues to react to carcinogens are discussed.—Biological Abstracts.

MISCELLANEOUS

FOSDICK, L. S., AND RAPP, G. W.: *The effect of amylolytic enzymes on acid production in saliva.* (*J. Dental Res.*, v. 23, p. 85, April, 1944).

Saliva was collected by paraffin stimulation. Pancreatic amylase was used as the test material. There was 100 per cent increase in acid formation when concentrations of 400 mg. per 100 cc. were used. A general trend toward faster acid production with high ptyalin index was found, though there were many exceptions to this. It was pointed out that the stimulation of acid production caused by pancreatic amylase could not be due to amylolytic activity because glucose was the sugar used and glucose is not affected by amylase.—R. L. Burdick.

Infectious Gastro-Enteritis: An Epidemiologic and Laboratory Study

By

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IN the course of studies on the etiology of various diseases attention has been directed repeatedly to the occurrence of cases of gastro-enteritis, "intestinal influenza," during or following severe epidemic infections of the respiratory tract and to a milder form of gastro-enteritis occurring sporadically and in explosive outbreaks remote from epidemics of influenza. A streptococcus which produced diarrhea and severe lesions of the gastro-intestinal tract electively was isolated in cases of gastro-enteritis during the pandemic of influenza of 1918 to 1920.¹ It is the purpose of this paper to record the epidemiologic and experimental data obtained in a study of a series of outbreaks of gastro-enteritis unassociated with severe infections of the respiratory tract.

EPIDEMIOLOGIC STUDIES

Altogether fifteen outbreaks of gastro-enteritis unassociated with infections of the respiratory tract have been studied over a period of eleven years. Eight occurred in hospitals, nurses' homes, hotels or convents and seven in private homes in the same city. Four outbreaks occurred in January, two in February, five in March, one in May, one in September and two in November. The number of cases studied in the different outbreaks ranged from five to twenty-two, or a total of 180 cases. Many more cases which were not studied occurred in remote homes during these outbreaks. The symptoms, duration and character of the disease in the different outbreaks were much alike and resembled closely those noted in the cases of gastro-enteritis which occurred in outbreaks reported by Boardman,² Spencer,³ Wildman,⁴ Fellman,⁵ Koehler,⁶ Veldee,⁷ Cary, Dack and Myers,⁸ and others.

The attacks began with sudden pain in the epigastrium and with general abdominal discomfort. Nausea and usually vomiting soon followed. In more severe cases profuse diarrhea occurred promptly, lasting usually several hours, sometimes longer. Prostration, general aching and headache of varying intensity were common manifestations. Fever usually was absent or slight, although occasionally it was high for a day or two. Chills or mild rigors occurred commonly. The leukocyte count was variable and of no diagnostic importance. Infections of nose or throat were slight or absent. Except for weakness, recovery usually was complete in twenty-four to forty-eight hours. There were no deaths. In two cases severe gastro-enteritis with bloody discharges from the onset progressed to ulcerations of the colon. One case of acute cholecystitis and one of acute appendicitis occurred. The disease was

too mild, of too short duration and too widespread to be due to a bacillus of the dysentery group, and dysentery bacilli were not isolable from stools or from water supplies. The course of the disease and the absence of organisms such as staphylococci excluded food intoxication, which the disease simulated. The sequence of occurrence of cases and the absence of neurotoxic symptoms distinguished the condition from botulism.

The disease often recurred at irregular intervals in mild epidemic waves in the city and surrounding country. Coincidentally with these, explosive outbreaks occurred in institutions and certain homes.

The water supply to six of the institutions in which outbreaks occurred was from artesian wells 500 feet (150 meters) or more deep and was not chlorinated. The plumbing system of each of the buildings where outbreaks occurred contained wholly, or in part, flushometer toilet valves. Other conditions permitting, cross-connections had been eliminated on account of previous outbreaks. Two of the institutions, which also were equipped wholly or in part with flushometer toilet valves, used the city water supply also obtained from artesian wells. The water supply of each of the seven private homes in which outbreaks occurred was likewise from the city. A history of lack of water pressure under stress was obtained and suction of air was demonstrated in each of these homes. In one household recurring illnesses, usually associated with diarrhea, were traced to back-siphonage through the under-water-level inlet of a bathtub. Fo-in that was placed in the bathtub, and which was drawn into the drinking water as suction was induced by turning on the cold water faucets at lower levels, was detected immediately in the water in this household and was present for several days following the usual use of the water supply. Outbreaks of gastro-enteritis no longer occurred in this household after the defect in the plumbing system had been rectified.

Cultures made from time to time from the water directly from the private and city artesian wells and more often from faucets or taps at the periphery repeatedly yielded streptococci (table 1) which usually resembled in virulence and otherwise the streptococci isolated from persons ill during current epidemics of gastro-enteritis, neuromyositis and respiratory infections. At the time of outbreaks of gastro-enteritis the strains isolated commonly produced diarrhea and lesions of the stomach and intestines of inoculated animals (table 2). Chlorination sufficed to render the water at the city plant free from streptococci but did not always suffice at the periphery where cases occurred.

The manner of occurrence and spread of outbreaks, the results of cultures and the course of the disease in

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the different epidemics studied are well illustrated in the following three outbreaks.

Outbreak A.—In a general hospital of 270 beds, twelve nurses and two physicians became violently ill with cramping pain in the abdomen, nausea, vomiting and diarrhea during the night of February 24-25 and the forenoon of February 25, 1936. Six frank cases and several mild cases occurred during the four subsequent days and then no cases occurred until March 8 to 13, when six additional cases occurred. Two physicians had had severe gastro-enteritis on February 12. An undetermined number of cases of headache, associated with mild gastro-intestinal symptoms not severe enough to prevent work, occurred during the outbreak. All persons who were stricken had eaten their meals in the general dining room of

milk served to patients. After completion of these studies bottled pasteurized milk was substituted for bulk milk. While a few cases of gastro-enteritis have continued to occur among patients and personnel from time to time since, no further explosive outbreaks have occurred.

Outbreak B.—On the morning of March 17, 1936, twenty-three nurses living in the nurses' home of a general hospital of 600 beds reported off duty because of illness characterized chiefly by gastro-intestinal symptoms, of which the most prominent were diarrhea, abdominal cramps, nausea and vomiting, chills, headache and general aching and weakness. These nurses became sick between 3 and 9 a.m. and on examination later in the morning had little or no fever but appeared acutely ill in varying degrees. A survey showed that no one food had been eaten in common on the previous day. A questionnaire was distributed on March 18 to all girls living in the nurses' home at that time, a total of 184. As had been suspected, many were found to have had mild symptoms which had not been reported. The following data were obtained: of twenty-five persons living on the first floor, nine (36 per cent) had become ill; of fifty-four living on the second floor, twenty (37 per cent) had become ill; of seventy-three living on the third floor, forty-two (58 per cent) had become ill; of thirty-two living on the fourth floor, twenty-eight (88 per cent) had become ill; of 103 living in the east half of the building, sixty-eight (66 per cent) had become ill; of eighty-one living in the west half of the building, thirty-one (38 per cent) had become ill.

Four girls who had not eaten supper in the hospital on the day previous to the outbreak became ill, but two of these had had symptoms since March 15, two days prior to the general outbreak. One girl who continued having cramps and slight diarrhea on March 19 admitted having drunk water from the faucet on the fourth floor of the east wing on March 18, the day after the outbreak and after the girls had been advised to use a different water supply.

Specific questioning of the two nurses in whom symptoms had developed on March 15 disclosed the fact that one living on the second floor, east wing, had had diarrhea first at 5 a.m. on March 15 and had noticed repeated difficulty in flushing the toilet of flushometer type in the bathroom of the east wing.

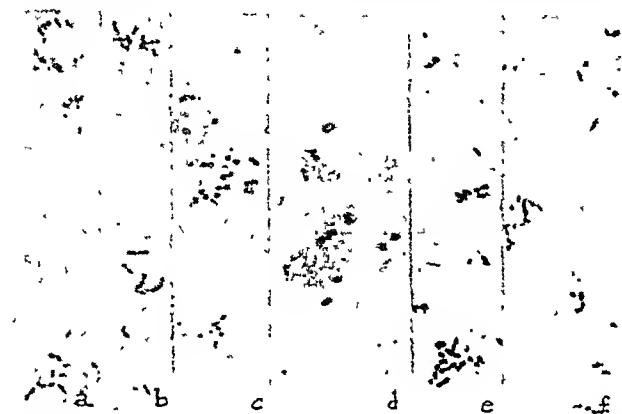


Fig. 1. Streptococci or diplostreptococci as isolated from (A) blood, (B) stool and (C) nasopharynx of patients; (D) air; (E) air after two animal passages and (F) water after one animal passage (Gram stain, $\times 1,000$).

the hospital. No frank cases occurred among patients and hospital personnel who had not eaten in the dining room.

The symptoms began suddenly; two persons fainted at the onset and all felt relieved first after profuse vomiting, sometimes of food eaten twenty-four hours before, and after several copious watery stools. The only article of food in common was pasteurized milk served in the dining room. The milk supplied to the entire hospital was pasteurized by the same large dairy. To patients it was delivered and served in individual half-pint (237 c.c.) bottles; to the general dining room it was delivered in ten-gallon (38 liter) bulk lots and was served through a common faucet from a small tank into which the bulk milk was poured before each meal. The milk in this tank and in delivery cans was not refrigerated during about two hours each at breakfast, luncheon and dinner. The milk left over in the tank after each meal period was drained and poured back into the delivery can, which was then replaced in the refrigerator until the next meal. The tank was cleansed after each serving period with water from the drinking supply and then rinsed with water heated in a tea kettle. The water supply throughout the hospital was not chlorinated and was derived from two private wells approximately 500 feet (150 meters) deep.

Bacteriologic examinations, made by the usual standard methods at irregular intervals over a period of years and at the time of this outbreak, of samplings of water directly from the wells and from delivery faucets or fountains at the periphery in the hospital never revealed contamination with colon or dysentery bacilli. By the use of brain-containing mediums, the organism to be described, which I have come to regard as the etiologic agent of epidemic gastro-enteritis, was isolated from the nasopharynx, stool and blood of patients, from each of six samplings of water directly from the well (always in small numbers), from fifteen of sixteen samples of water from taps in the hospital including all of four samples from the dining room tap, from the tank used to dispense the milk and in large numbers from left-over bulk milk used the day prior to the outbreak. The organism was not obtained in cultures from any of six previously unopened bottles of pasteurized



Fig. 2. Hemorrhagic lesions (A) in the intestines, (B) in the fundus and (C) in the cardiac orifice of the stomach of a rabbit forty-eight hours after intracerebral inoculation of the diplostreptococcus isolated from the water supply during an outbreak of gastro-enteritis ($\times 1\frac{1}{2}$).

The other girl, living on the fourth floor, east wing, in whom symptoms also developed on March 15, did not notice any difficulty in flushing toilets. I am indebted to Dr. George A. Lord for this detailed report of the outbreak.

The water supply to the hospital, where no cases occurred, and to the nurses' home was from a large standpipe tank kept full from one artesian well 500 feet (150 meters) deep and was not chlorinated. No recent changes in the plumbing system

had been made. The water had not been shut off for repairs. On inquiry a history was obtained of a lack of water pressure for the fourth floor during rush hours. All toilets in the nurses' home were equipped with flushometer type of valve in common use. Back-suction of air in water faucets and disappearance of residual water in one of the toilets on the fourth floor of the east wing was demonstrated when faucets and toilets on the lower floors were turned on. Back-suction of the water from the toilet bowl on the fourth floor occurred when the valve mechanism was in the closed position. A linear defect 1 cm. in length was found in the diaphragm of this valve. This lack of water pressure was found to be due, not to inadequate delivery capacity of the central supply pipe, but to partial closure of the main valve by someone unknown to the engineer in charge.

Bacillus coli (*Escherichia coli*) was isolated from samples taken on the fourth floor of the east wing the day after the outbreak but not from samples taken subsequently, or on other floors. A diplostreptococcus which produced diarrhea in animals was isolated by our method from nineteen (76 per cent) of twenty-five samples collected at the periphery at the time when cases occurred. Streptococci that did not produce diarrhea were isolated from fourteen (56 per cent) of the twenty-five samples obtained at the periphery and from two (33 per cent) of six samples obtained centrally, remote from the outbreak. The cultures from the water from the fourth floor of the east wing of the nurses' home, where most of the cases occurred, continued to yield the diplostreptococcus at intervals for a period of six weeks, despite repeated flushings of the water system. This organism disappeared within a few days after the leather gaskets of the flushometer toilet valves and the rubberized gaskets to all faucets were replaced by new ones. Cultures from macerated pieces of the old gaskets repeatedly yielded streptococci and diplostreptococci, even after drying.

Outbreak C.—During a mild outbreak of gastro-enteritis in the city, eleven of eighty-seven nurses who lived in a nurses' home became acutely ill on November 17, 1936, with cramping pains in the abdomen followed by nausea, vomiting and diarrhea. Seven of the eleven cases occurred on the third floor and five of these occurred in rooms at the peripheral end where a history of lack of water pressure was obtained. Three occurred on the second floor and one on the first floor. On inquiry it was found that one of the nurses who lived on the second floor had had an attack of gastro-enteritis two days previously. The nurses ate their meals at the dining room of the hospital mentioned in the account of outbreak A. No other cases occurred among the persons who ate in this dining room. All who became ill drank water from the faucets in their rooms. The water was from the chlorinated supply of the city. In this, as in other outbreaks, recovery was prompt and no additional cases occurred after the nurses had been instructed to drink water from near the inlet, cultures of which proved free from streptococci and diplostreptococci.

The toilets throughout the home were equipped with flushometer type valves. Increasing lack of pressure and back-suction of air under stress were demonstrated toward the periphery of the water supply pipe on the third, or upper, floor. These, as in outbreak B, were due, not to inadequate size of water pipes, but to partial closure of the main supply valve. With correction of this error and with installation of vacuum-breakers on the flush toilet valves explosive outbreaks of gastro-enteritis have not occurred since.

Cultures by our methods from the water supply at the inlet proved negative for streptococci, diplostreptococci and *Escherichia coli* but on the day after the outbreak cultures from six of seven samples of water obtained from faucets in the rooms where cases occurred yielded the diplostreptococcus. Gas-forming, gram-negative bacilli, presumably *Escherichia coli*, were isolated from one of the samples obtained on the third floor farthest from the inlet. As a control study, cultures were made of the water from faucets in another nurses' home of like size, in which other nurses who ate in the hospital dining room lived and where no cases occurred. The water supply was likewise from the city but tank toilets instead of the flush-type were used throughout the building. Streptococci or

diplostreptococci were not isolated from any of ten samples of water cultured, including a sample obtained at the inlet. Cultures from samplings of the city supply obtained at the plant likewise were negative.

LABORATORY STUDIES

Methods.—In order to isolate, if possible, the elusive inciting agent of this disease my colleagues and I applied the methods used in a study of other diseases.^{9, 10}

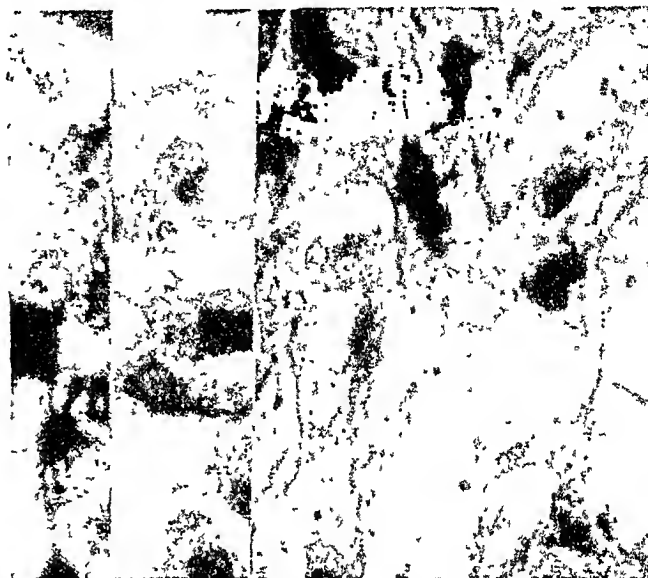


Fig. 3. Ovoids and diplococci in the wall of the hemorrhagic intestine of the rabbit referred to in figure 2, forty-eight hours after intracerebral inoculation of the diplostreptococcus isolated from water (x1,000).

Cultures of nasopharyngeal swabbings, stool and blood clot of patients and of suspected material such as food, milk, water and air were made routinely on blood-agar plates and in tall columns of dextrose-brain broth. Animals were inoculated with cultures of suspected organisms as isolated with water, with filtrates of stools, and with filtrates of dextrose-brain broth and chick-embryo medium cultures of streptococci from air and water. Cutaneous tests were made at the time of acute attacks among persons and subsequently with the euglobulin fraction of serums of horses immunized, respectively, with the diplostreptococcus of chronic ulcerative colitis and streptococci from other diseases. Precipitation and agglutination tests were made with the serum of patients and different streptococcal antisera prepared in horses.

The clue as to which of a number of organisms isolated might have etiologic significance was obtained on their injection into animals. Only streptococci or diplostreptococci isolated in dextrose-brain broth consistently produced diarrhea and lesions of the gastrointestinal tract.

Cultures from the stool were made in dextrose-brain broth from highly diluted suspensions in saline solution before heating and after heating to 50°C for one hour, and by the serial dilution method alternately in dextrose-brain broth and dextrose-brain agar.¹¹ Cultures from the blood were made by partially macerating the clot after decanting the serum, and planting into freshly prepared dextrose-brain broth. The samples of water were collected routinely under sterile precautions from flamed faucets or taps in amounts of approximate-

ly 180 c.c. in tall nursing bottles. Approximately 30 c.c. of the water, uncentrifuged, or this amount containing the centrifuged sediment, was planted into about 160 c.c. of 0.2 per cent dextrose broth to which approximately 15 gm. of brain substance had been added before autoclaving, and into like amounts of 0.2 per cent dextrose broth without addition of brain tissue. Three cubic centimeters was also added to tall tubes of dextrose-brain broth. Two tubes (40 c.c.) of dextrose-brain broth usually were added to the remaining water and incubated. In special instances serial dilution cultures were made of water and stools in dextrose-brain agar. All inoculated mediums were incubated at 33 to 35°C. Cultures from the air were

brain broth; guinea-pigs received 0.05 to 0.1 c.c. intracerebrally and mice were given 0.03 c.c. of the same dilution intracerebrally or 1.2 to 2.5 c.c. of the undiluted culture intraperitoneally. One to 2.0 c.c. of filtrates was inoculated intracerebrally into rabbits, 0.2 c.c. into guinea-pigs and 0.03 c.c. into mice. Cultures were made routinely in dextrose-brain broth from blood and brain of the animals that had succumbed. In order to determine whether a virus might be the cause of this disease, rabbits, mice and guinea-pigs were inoculated intracerebrally with filtrates of stools, of dextrose-brain broth and chick-embryo medium cultures of the streptococci from water and air, and of emulsions of the brains of animals that had succumbed late to inocula-

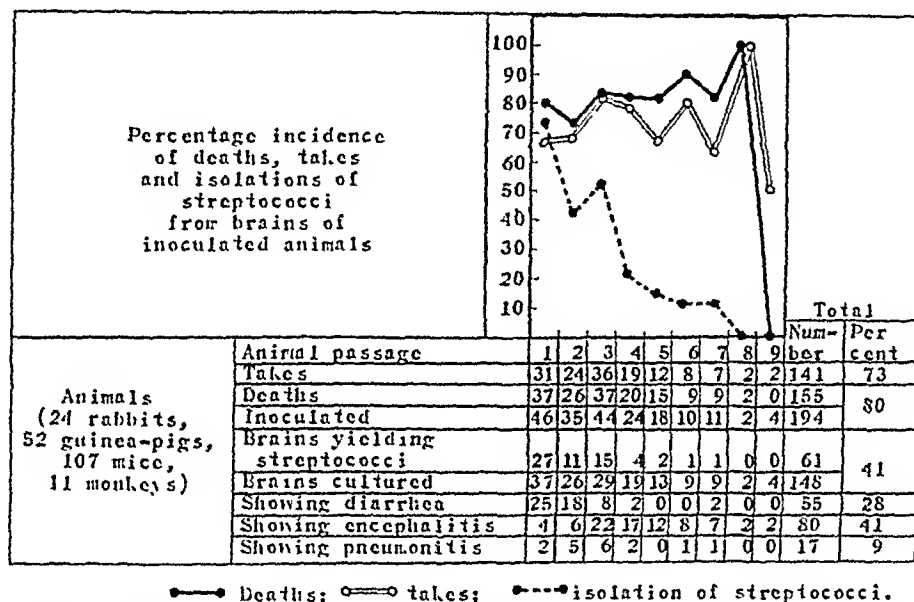


Fig. 4. Results among animals following intracerebral inoculation of streptococci isolated from nasopharynx, stools, water supplies and air in relation to epidemic gastro-enteritis and following successive passage of emulsions or filtrates of emulsions of the brains of animals that had succumbed. For explanation of "takes" see text, pp. 387-388

made by drawing air at the rate of 250 c.c. per minute for one to twenty-four hours through 150 c.c. each of dextrose-brain broth, dextrose broth and chick-embryo medium, and 10 c.c. of distilled water, and by exposing to the air blood-agar plates and Perti dishes containing these mediums.

At first rabbits were inoculated, either intravenously or intracerebrally, with different organisms as isolated from nasopharynx, stool and blood of patients during attacks and from water and air during outbreaks. The intracerebral route was found the more effective and hence intracerebral inoculations were given routinely to measure the infecting power of the different strains on isolation. Therefore, human volunteers were not given cultures, as was done by Cary, Dack and Myers to prove etiologic relationship of a similar green-producing streptococcus which they isolated from sausage and which was the cause of an outbreak studied by them. Rabbits were given routinely, far forward in the right frontal lobe, 0.1 c.c. of a 1:1,000 or a 1:200 dilution of eight to eighteen hour cultures in dextrose-

tions of the diplostreptococcus or streptococcus.

Cutaneous tests were made by intradermal injection of 0.03 or 0.05 c.c. of a 10 per cent saline solution of the euglobulin fraction of the serum of horses hyperimmunized with streptococci as isolated in different diseases. Erythematous-edematous reactions to the euglobulin fraction of the antiserum prepared with the diplostreptococcus of ulcerative colitis (Bargen) occurred within ten minutes after such injections, when no reactions or lesser ones occurred to unrelated antisera and normal horse serum. Such reactions were taken to indicate the presence of streptococcal antigen in the skin or blood of the patient, immunologically related to the streptococci used to prepare the reacting antibody.^{12, 13}

Agglutination tests were made, by methods previously described,^{9, 10} with pure cultures of the streptococcus or diplostreptococcus from nasopharynx, blood or stool of patients, from the water supply, from the air and from animals that had succumbed to inoculations of these strains, with tenfold dilutions of the ulcerative

colitis and control antisera and with twofold dilutions of convalescent serum. Agglutination of streptococci by antisera was considered as positive when greater in degree or when agglutination occurred at higher dilutions of the serum of patients convalescing from gastro-enteritis than with control normal sera or sera from patients having diseases other than gastro-enteritis or ulcerative colitis.

Interphase precipitation tests were made in small precipitation tubes with as little admixing as possible, by superimposing the clear sera of fasting patients over the respective antisera prepared with the diplostreptococcus of ulcerative colitis and streptococci isolated in studies of encephalitis, poliomyelitis and arthritis and with types I, II and III pneumococci. The setups were incubated at 35°C. for one and a half hours and then placed in the refrigerator overnight. Readings were made in a dark room under a strong light against a nonreflecting, black velvet background.

Results of cultures.—The results of cultures from persons, water and air are summarized in table 1. The higher incidence of isolation in dextrose-brain broth of streptococci or diplostreptococci from water and air at the time of attacks or outbreaks than remote from outbreaks is well shown. Cultures in dextrose-brain broth from water and air at the time of outbreaks commonly yielded gram-negative diplostreptococci with which diarrhea and lesions of the intestines were produced in animals. The organisms grew out diffusely in this medium in forty-eight hours, without sediment and without production of acid. Growth was greatest in the upper layers. In cultures from water the diplostreptococci often were mixed with gram-negative bacilli belonging to the *Pseudomonas* group. *Shigella dysenteriae* was not isolated from nasopharynx, blood or stool of patients or from the water supplies and air. I learned to suspect the presence of the gram-negative diplostreptococcus in dextrose-brain broth cultures, especially old cultures, by a peculiar musty odor, described by Veldee, resembling that of the water responsible for the extensive outbreaks. Boiling these cultures caused the odor to disappear, as did boiling the water in the epidemics reported by him.

The gram-negative diplostreptococci and streptococci almost never were isolated directly from water and air in cultures on blood-agar plates or in plain or dextrose agar and were isolated only occasionally in dextrose broth. After growth in dextrose-brain broth they were readily cultivable in these less favorable media. On blood-agar plates the gram-negative diplostreptococci produced smooth, grayish brown, glistening, nonhemolyzing colonies about twice the size of streptococcal colonies. Smears from single colonies and from dextrose-brain broth revealed gram-negative diplococci sometimes occurring in short chains. The streptococci produced small, nonadherent, grayish colonies surrounded by a greenish zone of partial hemolysis on blood-agar plates.

At first I was puzzled over the fact that the gram-negative diplostreptococci so commonly isolated from water and air during outbreaks of gastro-enteritis could

not be isolated from the nasopharynx and that they were isolable only occasionally from stools, except those at the very onset of attacks, and only once from the blood of a patient. Gram-negative streptococci or diplostreptococci, with which diarrhea also was produced consistently, were isolated instead. The experiments on animals furnished the clue. Cultures from brain and blood of animals that had succumbed to diarrhea following inoculations of the gram-negative diplostrep-



Fig. 5. Perivascular and parenchymatous edema and round-cell infiltration of the ependyma of the brain of two *Macacus rhesus* monkeys that had succumbed with symptoms of poliomyelitis eight days after intracerebral and intraspinal inoculation of an emulsion of brain and spinal cord of a monkey that also had succumbed to poliomyelitis following inoculation of an infectious agent (in the third animal passage) derived from the streptococcus isolated from the water supply in an outbreak of gastroenteritis. Cultures of the emulsion of brain and spinal cord of these monkeys and of the emulsion with which they were inoculated proved sterile (hematoxylin and eosin, x170 and 125).

cocci yielded gram-positive streptococci only or mixtures of gram-positive streptococci consistently following inoculations of mixed cultures of the gram-negative diplostreptococci and gram-negative bacilli belonging to the genus *Pseudomonas*, of pure cultures in dextrose-brain broth as determined by stained films and by plating, and of pure cultures from single colonies on blood-agar plates and from single colonies in highly diluted cultures in soft dextrose-brain agar.¹¹

In staining reactions, grouping, size and shape, the organisms isolated from these animals resembled those isolated from patients. They likewise produced diarrhea and lesions in the intestines on reinjection into animals. Growth in vitro in serum-broth often sufficed to convert the gram-negative diplostreptococci into gram-positive diplostreptococci. Moreover, the gram-negative diplostreptococci isolated from water and air and the gram-positive streptococci and diplostreptococci isolated from patients and from animals inoculated with the gram-negative diplostreptococcus were alike or similar in their agglutinating properties. I concluded, therefore, that the gram-positive streptococcus or diplostrepto-

coccus isolated from patients represented gram-negative diplostreptococci which had undergone the same change as occurred in inoculated animals. In figure 1 the morphologic characteristics of the diplostreptococci isolated directly from persons (a, b, and c), air (d, before animals passage, and e, after two animal passages) and water (f, after one animal passage) are well shown.

Results of studies on animals with the streptococcus and diplostreptococcus.—Diarrhea developed usually within twenty-four hours, and sometimes as early as eight hours, after intracerebral inoculation of the freshly isolated diplostreptococcus or streptococcus or of filtrates. Among rabbits receiving live cultures, diarrhea lasted for a variable period, usually from one to three or seven days. Among rabbits, transient diarrhea often followed intracerebral inoculation of 0.5 to 1.0 c.c. of the filtrate of young, actively growing cultures in dextrose-brain broth. Among mice this sign was of

a far higher incidence of diarrhea and of gross lesions of stomach or intestines among rabbits that received injections of strains from patients that had active gastro-enteritis, from the water supply at the time of outbreaks, and from air at the time of outbreaks than following similar inoculations of streptococci from persons having diseases other than those of the gastro-intestinal tract, from the same water supplies remote from outbreaks or from miscellaneous water supplies also remote from outbreaks.

The incidence of diarrhea and death among mice (table 3) following intracerebral or intraperitoneal inoculation of the streptococcus or diplostreptococcus isolated from patients, as well as from water and air during outbreaks, also was far higher than following inoculation of streptococci or diplostreptococci from water remote from outbreaks.

Most animals that recovered from the primary attack

Table 1

Isolation in dextrose-brain broth of streptococci and diplostreptococci from patients, drinking water and air during outbreaks of gastro-enteritis

Source of material cultured		Cases or specimens	Per cent yielding			
			Streptococci or diplostreptococci	Micrococci	Bacilli	
					Gram-positive	Gram-negative
Patients during acute attacks (86 cases)	Nasopharynx	72	86*	8	0	4
	Blood	42	17	7	5	0
	Stool	28	75	14	04	100
Water supply	During outbreaks	131	85	6	47	76
	Central supply	37	65	11	62	76
	Remote from outbreaks	79	58	5	55	63
	Central supply	31	48	6	45	100
Indoor and outdoor air	During outbreaks	45	42	58	91	16
	Remote from outbreaks	39	13	69	95	8

* In all tables, fractions of percentages are given to the nearest whole number

shorter duration, often occurring only shortly before death. Rabbits that had severe attacks became weak, were easily fatigued and lost weight rapidly. Symptoms of poliomyelitis occurred in a few instances. Suppurative meningitis was not found in any.

After death there were found liquid contents in the lumen, cloudy swelling of the wall throughout the intestinal tract, and small hemorrhages in the mucous membrane or submucosa, especially of the small intestine and the stomach (fig. 2). Stained films of the exudate overlying hemorrhagic lesions often revealed large numbers of the diplostreptococci. Sections of the walls of the stomach and intestines showing hemorrhages revealed dilated capillaries; extravasated erythrocytes and circumscribed regions of poorly staining cells; variable, but usually slight, cellular infiltration, and necrosis. Sections stained by Gram's method, but only partially decolorized with alcohol, revealed ovoids and diplococci, often in large numbers, adjacent to, or in, regions showing hemorrhages or poorly staining cells (fig. 3).

The incidence of symptoms, deaths and lesions among rabbits following inoculation of the streptococcus or diplostreptococcus is summarized in table 2. There was

remained well indefinitely but were not immune to subsequent inoculation of the diplostreptococci. Cultures from pipettings from the brain of rabbits and mice that had succumbed soon after intracerebral inoculation usually yielded short-chained, gram-positive streptococci mixed with gram-negative diplostreptococci, if the latter had been inoculated; the corresponding procedure for animals that had died seven or more days after inoculation usually yielded pure cultures of streptococci or no growth. Some animals remained well for a week or ten days after inoculation and then diarrhea developed and continued until death. This corresponded to the common late occurrence of cases during outbreaks and was thought suggestive of a viral infection.

Accordingly, rabbits, guinea-pigs, mice and monkeys were inoculated intracerebrally with old cultures of the streptococcus or diplostreptococcus in chick-embryo medium or with filtrates of these, in a manner previously used.^{14, 15, 16} Filtrates and emulsions of the brains of animals that had succumbed late were inoculated intracerebrally in subsequent passages. Control animals were inoculated with the corresponding sterile chick-embryo medium and filtrates thereof and with emulsions and filtrates of emulsions of the brains of normal

animals.

The streptococci or diplostreptococci inoculated in the first passage were isolated from the nasopharynx or stool of patients during the acute stage of the disease, from water supplies and from indoor and outdoor air during outbreaks. They had been subcultured in rapid succession ten to twenty-seven times in dextrose-brain broth, representing a hundredfold dilution of the original inoculum at every subculture, before they were inoculated into the autoclaved chick-embryo medium. The results obtained in nine successive passages through animals (twenty-four rabbits, fifty-two guinea-pigs, 107 mice and eleven monkeys) are summarized in figure 4.

Diarrhea, with or without lesions of the stomach and intestines, developed late in twenty-five, symptoms and lesions of encephalitis in four and pneumonitis in two cases in the first passage. In other words, there were what may be considered as "virus takes" in a total of thirty-one of the forty-six animals inoculated in the primary passage. Of the forty-six animals, twenty-eight

For two passages the incidence of pneumonitis also increased but then it decreased and ultimately disappeared. All but three of the seventeen animals in which lesions of lungs (pneumonitis) had developed in these passage experiments were inoculated with a culture of streptococcus isolated from the stool of a patient in whom severe diarrhea had developed while the patient was having symptoms of respiratory influenza, or with brain material derived therefrom. Symptoms and lesions of more than one type of disease developed among some of the inoculated animals, as they had among the respective patients.

Altogether, emulsions of the brains of forty-one animals and filtrates of emulsions of the brains of eleven animals were used in the second to the ninth serial passages. Of the nineteen animals that received filtrates of brain emulsions, "takes" occurred in sixteen animals (six mice, five guinea-pigs, three rabbits and two monkeys) in from three to twenty-one days following inoculation. As mortality rate and "takes" increased

Table 2

Symptoms, deaths and lesions of rabbits following intracerebral inoculation of the streptococcus or diplostreptococcus

Source of the streptococcus or diplostreptococcus		Strains	Rabbits						
			Inoculated	Per cent in which diarrhea developed	Deaths		Lesions of stomach or intestines, per cent*	Streptococci from	
					Number	Per cent of inoculated		Brain, per cent*	Blood, per cent*
Patients having	Gastro-enteritis	64	110	69	71	65	55	61	21
	Diseases other than of gastro-intestinal tract	40	90	4	73	81	15	71	16
Drinking water	Time of outbreaks	101	175	65	108	62	71	50	25
	Remote from outbreaks	60	94	9	40	43	18	43	40
Miscellaneous water supplies	Remote from outbreaks	38	88	8	40	45	15	58	18
Indoor and outdoor air	Time of outbreaks	25	148	44	97	66	44	43	44

* Percentages figured on the basis of animals that died.

received old chick-embryo cultures and eighteen received filtrates of the chick-embryo cultures of the streptococcus. Symptoms and lesions of gastro-enteritis, pneumonitis or encephalitis ("takes") developed in three to twenty-one days among twenty-three of the twenty-eight animals that had received culture, including three monkeys, and in eight of the eighteen that had received filtrate (two rabbits, two mice and four guinea-pigs). Among the remaining fifteen animals it was not possible to determine whether symptoms, lesions or deaths were due to "virus takes" or to the streptococcus as such. On successive passage of emulsions or filtrates of emulsions of the brains of animals in which symptoms had developed in from three to twenty-one days and that were anesthetized for transfer of brain material, the incidence of development of diarrhea and lesions of the gastro-intestinal tract declined, whereas symptoms and lesions of encephalitis, especially among mice, increased

through eight consecutive passages of emulsions or filtrates of emulsions of brains, the incidence of isolations of streptococci diminished and then disappeared. The infectious agent derived from the streptococcus was lost in the ninth passage.

Sections of the brains and spinal cords of animals that had succumbed to serial passage of the infectious agent revealed varying degrees of degeneration and ependymal parenchymatous and perivascular round-cell infiltration, well illustrated in figure 5. The results in these serial passage experiments were similar to those obtained in other studies.^{11, 15, 16}

No instance of diarrhea, encephalitis or pneumonitis occurred among control animals after intracerebral inoculation of sterile chick-embryo medium or filtrates thereof, and emulsions or filtrates of emulsions of the brains of normal animals.

Streptococcal antigen in air.—As shown in table 4,

precipitation tests were made with antisera from horses immunized, respectively, with the diplostreptococcus of chronic ulcerative colitis and streptococci from other diseases, using as antigens, twelve samples of water, rendered isotonic with salt solution, after air had been bubbled through them for one to twenty-four hours. Six of the twelve antigens represented samplings from indoor and outdoor air in November, 1938, during an outbreak of gastro-enteritis and the other six represented samplings of outdoor air obtained in the same manner from the same places during December, after the outbreak of gastro-enteritis had disappeared and epidemic influenza had appeared. Of the former group, one sampling represented overnight air of a large room where four persons having gastro-enteritis slept, one represented the air of a room crowded with well persons at the time of the outbreak, and the remaining four samplings represented outdoor air in the general region where cases occurred. One of the samples of outdoor air was obtained 10 feet (3 meters) from the side of a

of air had been drawn through dextrose-brain broth, cultures of streptococci or diplostreptococci were obtained from each of six samples during the epidemic of gastro-enteritis and the streptococcus having pneumotropic virulence was isolated from four of the samples after gastro-enteritis had subsided and influenza had appeared.

Four of the six strains of streptococci isolated in dextrose-brain broth during the epidemic of gastro-enteritis produced diarrhea among animals but did not produce lesions of lungs. Two produced diarrhea and severe hemorrhagic edema of lungs. None of four strains of streptococci isolated during the epidemic of influenza produced diarrhea but instead all produced hemorrhagic edema of lungs with or without bronchopneumonia.

Results of serologic studies.—The erythematous reaction to intradermal injections of the euglobulin fraction of the respective antistreptococcal sera in the case of persons ill with infectious gastro-enteritis nearly

Table 3
Diarrhea and deaths among mice following intracerebral or intraperitoneal inoculation of the streptococcus or diplostreptococcus

Source of material inoculated		Strains	Mice			
			Inoculated	Diarrhea, per cent	Died	
					Number	Per cent of inoculated
Patients having epidemic gastro-enteritis		37	63	46	47	75
Drinking water	Time of outbreaks	97	273	23	182	67
	Remote from outbreaks	50	154	3	79	51
Miscellaneous water supplies remote from outbreaks		48	151	0	74	49
Indoor and outdoor air at time of outbreaks		39	146	27	106	73

building sixteen stories from the street level, the air being drawn continuously through water for twenty-four hours, and three represented air from the front end of an automobile during three drives of 20, 96 and 196 miles (32, 154 and 306 kilometers), respectively, the air being drawn through water by tapping the vacuum line.

The antigens absorbed by the water through which air had been bubbled during the outbreak of gastro-enteritis were more closely related immunologically to the diplostreptococcus isolated in studies of chronic ulcerative colitis and the streptococcus isolated in studies of ulcer of the stomach or duodenum (precipitation at the interphase being 100 and 90 per cent, respectively) than to the streptococci associated with influenza, encephalitis, poliomyelitis or arthritis. Each of the four samples that yielded streptococci in the corresponding culture in dextrose-brain broth gave an interphase reaction with the influenza antistreptococcal serum.

Cultures in dextrose-brain broth from the different samples of water after air had been bubbled through them almost never yielded streptococci or the gram-negative diplostreptococcus but, after the same amount

always was greatest to the euglobulin fraction of the serum of horses that had been immunized with the diplostreptococcus of chronic ulcerative colitis, the most closely related disease represented by the antisera used. The average reactions in square centimeters to the different antisera are summarized in table 5. It will be seen (1) that the reaction among patients having acute gastro-enteritis or among those ill with chronic ulcerative colitis was greatest to the ulcerative colitis euglobulin, (2) that the reaction among persons having other diseases (encephalitis, chronic infectious arthritis, and ulcer of the stomach or duodenum) was greatest to each of the euglobulins from the homologous antisera, (3) that well persons reacted only slightly and about equally to the different euglobulins, and (4) that the euglobulin fraction of antipneumococcus sera and normal horse serum caused little or no reaction.

The results of the precipitation reactions (table 6) were corroborative of the cutaneous reaction. Antigen related to the diplostreptococcus of ulcerative colitis was demonstrable most often in the serum of patients at the time of the acute attack and as recovery occurred it

tended to disappear. The incidence of positive precipitation reactions with the control serums was highest to each of the homologous antisera prepared with streptococci isolated from cases of the respective diseases.

The diagnostic value of the cutaneous and precipitation reactions in these outbreaks was emphasized in a study of a small outbreak of food poisoning traced to turkey dressing. Each of four persons who ate of the dressing had abdominal cramps, nausea, vomiting and

that had succumbed

The results of studies of agglutination with the serum of patients during convalescence and the diplostreptococcus isolated from patients, water and air during epidemic are summarized in table 7. Well-marked specificity is shown.

COMMENT AND SUMMARY

A study of a series of outbreaks of gastro-enteritis resembling, and usually erroneously considered to be, food poisoning is reported.

Table 4
Precipitation reaction between streptococcal antisera and bacterial antigen from air

Antigens from air	Antigens	Tests	Per cent of positive reaction in antisera prepared with streptococci isolated in studies of:						Per cent of positive reactions in normal horse serum
			Chronic ulcerative colitis	Ulcer of stomach or duodenum	Influenza	Encephalitis	Polio-myelitis	Arthritis	
During an outbreak of gastro-enteritis	6	10	100	90	40	30	10	30	0
After the outbreak of gastro-enteritis had disappeared and epidemic influenza had appeared	6	6	17	17	67	17	0	0	0

profuse diarrhea about twelve hours later, whereas two persons who did not eat dressing remained well. Cutaneous reactions to injection of the ulcerative colitis

Streptococci or diplostreptococci with which diarrhea and lesions in the gastro-intestinal tract have been produced among animals have been isolated consistently

Table 5
Erythematous reactions to intradermal injection of the englobulin fraction of antistreptococcal sera

Groups tested		Cases	Average reaction (sq. cm) to englobulins prepared with streptococci from:					
			Chronic ulcerative colitis	Encephalitis	Arthritis	Ulcer of stomach or duodenum	Control sera	
							Types I, II and III pneumococci	Normal horse
Acute gastro-enteritis	5 major outbreaks	94	9.8	6.9	4.7	7.2	1.8	1.2
	10 smaller outbreaks	26	1.2	9.8	4.6	7.8		1.1
	Total	120	10	7.5	4.7	7.3		1.2
Chronic ulcerative colitis		13	10	5	5	4	1	1
Encephalitis		92	3	6	3		1	0
Chronic infectious arthritis		42	3	3	8	3	2	0
Ulcer of stomach or duodenum		39	10	5	4	11	0	0
Well controls		25	1.2	1.2	1.1	1.3		0.6

englobulin and the precipitation reaction between the serum of the persons ill and the ulcerative colitis antiserum proved negative. A staphylococcus was isolated from the dressing and from the blood of one patient. Both strains on intracerebral inoculation into rabbits produced diarrhea, prostration and death. The staphylococcus was isolated from the brains of the animals

by special methods from nasopharynx, stool and blood of patients, from the water supply of patients and from the air of rooms occupied by persons stricken. Ordinary mediums in general use usually did not suffice for initial isolations. *Escherichia coli* was isolated rarely from water supplies and *Shigella dysenteriae* was never isolated from water supplies or stools of patients

ill with gastro-enteritis. The total bacterial counts as determined by plating in agar were low in the case of water supplies yielding the streptococcus or diplostreptococcus at the time of outbreaks. Chlorination sufficed to render the water of the city free from the streptococcus and diplostreptococcus at the plant but did not suffice at the periphery where cases occurred. Mild contamination with the diplostreptococcus of the water from wells 500 feet (150 meters) deep, while seemingly responsible for isolated sporadic cases, was never suf-

The occurrence of the outbreaks studied should not be interpreted as indicating subaverage sanitary conditions in the city and institutions in question. The water supplies at their source were found free from *Escherichia coli* and *Shigella dysenteriae* by the health department as determined by the well-established methods of water analysis. The occurrence of similar and much larger institutional and community outbreaks of gastro-enteritis, some traced to water supplies, and their disappearance, as in the outbreaks studied, on correction

Table 6

Precipitation reaction between serums of patients having acute epidemic gastro-enteritis and of controls and the serum of horses immunized with the diplostreptococcus isolated in studies of chronic ulcerative colitis and of other diseases and control serums

Source of serums (antigens)		Cases	Percentage incidence of positive reactions with					
			Antiserums prepared with streptococci isolated in studies of				Control serums	
			Chronic ulcerative colitis	Encephalitis	Polio-myelitis	Arthritis	Types I, II and III pneumococci	Normal horse
Cases of gastro-enteritis in 5 major outbreaks	During acute attack	71	82	32	10	42	1	0
	4 to 5 days following acute attack	71*	28	20	14	18	0	1
	8 to 14 days following acute attack	64†	22	22	16	26	0	0
Cases of gastro-enteritis during acute attack in minor outbreaks in hospitals, nurses' homes, convents and private homes.		66	88	26	15	21	0	3
All cases during acute attacks		137	85	29	15	31	0	2
Controls	Encephalitis	30	20	70	33	23	0	0
	Polio-myelitis	28	11	46	86	15	0	0
	Arthritis	34	32	25	24	85	0	0
	Well persons	42	2	2	0	5	0	0

* Some seventy-one cases from which blood was obtained during acute attack.

† Sixty-four of the seventy-one cases.

ficient to cause a major outbreak except as it led to contamination of articles of food, such as milk (outbreak A). Peripheral "autogenous" contamination of the water supply through flushometer toilet valves or other sources of fecal contamination was responsible for at least two major outbreaks (outbreaks B and C). In one household recurring outbreaks of gastro-enteritis were traced to back-siphonage through the under-water-level inlet of a bathtub.

Evidence has been adduced which indicates that the widely disseminated occurrence of cases of gastro-enteritis at certain seasons may be air-borne or due to mildly contaminated water and that explosive outbreaks, such as reported by Boardman, Spencer, Wildman, Koehler and Veldee and those under study, were due to water badly contaminated at the periphery of water systems with the streptococcus or diplostreptococcus having specific affinity for the gastro-intestinal tract.

of existing errors in plumbing and other conditions have been reported repeatedly.^{1, 2, 3, 4, 6} The part that is new in this study is the isolation, by the special methods used, of what seems to be the causative agent.

A filtrable, infectious agent resembling virus developed in chick-embryo medium cultures of the streptococcus and diplostreptococcus of ulcerative colitis. With this agent the disease picture of gastro-enteritis was mainly produced on several successive passages through animals, after which symptoms and lesions of encephalitis supervened. As this occurred, the incidence of isolations of streptococci progressively decreased.

The streptococcus and diplococcus isolated in this study were closely related to the diplostreptococcus of ulcerative colitis (Bargen). Streptococcal antigen was demonstrated in the skin of patients by intradermal injection of the euglobulin fraction of the ulcerative colitis antistreptococcal serum, and in the serum of patients during the acute stage of the disease and in

washings from the air during epidemics by the precipitation reaction with the ulcerative colitis antistreptococcic serum. Specific agglutinins for the streptococcus and diplostreptococcus were demonstrated in the serum of patients during convalescence.

The data obtained indicate (1) that the usual, relatively mild form of epidemic gastro-enteritis is infectious; (2) that a diplo-streptococcus which dissociates

into an alpha streptococcus on animal passage, closely related antigenically and in virulence to the diplostreptococcus of ulcerative colitis and more distantly to streptococci associated with epidemic "intestinal" and "respiratory" influenza, is the inciting agent in primary cases and (3) that a filterable infectious agent derived from the streptococcus or diplostreptococcus causes the manifestations in secondary or late cases.

Table 7

Agglutination of the streptococcus or diplostreptococcus by the serum of patients convalescing from gastro-enteritis

Serum	Source of strains	Strains tested	Agglutination tests		
			Number	Positive	
				Number	Per cent
57	Patients	42	210	175	83
48	Water	24	142	114	80
28	Air	6	46	28	61
23	Control	22	116	6	5

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Proceedings of The New York Diabetes Association

April 25, 1944

"Surgical Treatment of Hyperthyroidism in Diabetes"

... Charles Gordon Heyd, M.D., New York Post-Graduate Hospital

Discussion: Charles G. Child, III, M.D., New York Hospital; Elliott P. Joslin, M.D., Boston, Mass.

"Preliminary Report on Amputation Below the Knee in the Diabetic"

... Samuel Silbert M.D., Mt. Sinai Hospital

Discussion: Thomas J. O'Kane, M.D., Morrisania City Hospital; Elliott P. Joslin, M.D., Boston, Mass.

"The Medical Pre and Post Operative Treatment of Surgical Diabetics"

... Elliott P. Joslin, M.D., Boston, Mass.

"Experiences with Penicillin in Diabetic Gangrene"

... Francis D. Moore, M.D., Boston, Mass.

Discussion: Edward Tolstoi, M.D., New York Hospital; Louis Bauman, M.D., Presbyterian Hospital; George E. Anderson, M.D., Brooklyn Hospital.

Dr. Beverly Chew Smith, Chairman of the Committee on Surgery, presiding.

Dr. Smith:

THIS meeting is the annual meeting of the Surgical Section of the New York Diabetes Association. The first paper to be presented will be given by Dr. Charles Gordon Heyd of the New York Post-Graduate Hospital entitled "Surgical Treatment of Hyperthyroidism in Diabetes".

"Surgical Treatment of Hyperthyroidism in Diabetes", Charles Gordon Heyd, M.D.

Diabetes mellitus and hyperthyroidism, either primary or secondary, are two separable and distinct disease entities. The two conditions many times simulate each other clinically but each is adversely affected by the other. The normal individual has an adequate amount of insulin supplied by his own pancreas. The diabetic patient cannot produce sufficient insulin and there is an insulin deficiency. The hyperthyroid patient does produce sufficient insulin but has an excess of thyroxin. Therefore, when the two conditions, diabetes and hyperthyroidism, are combined we have two clinical entities fundamentally different in chemistry and mutually antagonistic. Hyperthyroidism with its elevated basal metabolism and increased glycogenolysis imposes an added burden upon the inefficient carbohydrate metabolism of the diabetic.¹

Hyperthyroidism will not initiate a true diabetes but it will greatly exaggerate a pre or co-existing diabetic state because thyroxin is an active glycogenolytic agent and also stimulates gluconeogenesis—the production of carbohydrate from non-carbohydrate sources, e.g., protein.

Some of the beneficial effects of insulin are due to its inhibitory action on both glycogenolysis and gluconeogenesis. It follows that the action of insulin and thyroxin are antagonistic. Hence, insulin lack—diabetes mellitus and thyroxin excess, hyperthyroidism, are basically different.

It would seem that an adenomatous goiter with hyperthyroidism is a diabetogenous factor. Regan and Wilder² found that 5.6 percent of all patients with secondary hyperthyroidism (adenoma) had diabetes which is over three times

the incidence of diabetes in all new patients at the Mayo Clinic. In contrast only 1.7 percent of the patients with adenomatous goiter but without hyperthyroidism had diabetes. This is the same incidence of diabetes as in all new patients registered and almost identical with the percentage of patients with primary hyperthyroidism (Graves' disease or exophthalmic goiter) who had diabetes. Diabetes is complicated by adenomatous hyperthyroidism three times more frequently than by exophthalmic hyperthyroidism. Since adenomatous (secondary) hyperthyroidism is of much longer duration than exophthalmic hyperthyroidism, Regan and Wilder make the comment "the longer the duration of the hyperthyroidism the greater the incidence of diabetes".

Glycosuria in some degree and at some time or other will probably be present in almost every patient with hyperthyroidism. This glycosuria is sequential to a preceding hyperglycemia and is the result of the depletion of the liver glycogen stored by the excess thyroxin of the hyperthyroid state. In the presence of hyperthyroidism glucose is rapidly absorbed from the gastrointestinal tract. Furthermore, under the influence of thyroxin there is a rapid depletion of the glycogen in the liver thus increasing the hyperglycemia. In addition, there is a constant production of new carbohydrate from non-carbohydrate stores; this again leads to an increase in the hyperglycemia. Hyperthyroidism frequently produces an abnormal sugar tolerance curve which closely resembles that of the diabetic. There is, however, one striking difference between the sugar tolerance curve in the diabetic as compared to the hyperthyroid patient. In diabetes mellitus the fasting or control blood sugar is usually distinctly elevated above the normal, whereas in hyperthyroidism a normal fasting blood sugar is the rule, even though the tolerance curve may be abnormal.³

An individual with hyperthyroidism has a marked acceleration of combustion and demands an increased intake of food. If that individual has a normal pancreas, there will be no diabetes although glycosuria will be present at some time. If, however, the hyperthyroid patient has a diseased pancreas or abnormal insulinogenic mechanism there will be accelerated combustion with insulin deficiency. The combination of excess thyroxin and diminished insulin activates a latent diabetic and projects a mild diabetic into a severe diabetic. These two conditions essentially distinctive should not be allowed to exist or to continue in the same patient. Insulin effect is destroyed by thyroxin and large diet, and insulin cannot control a diabetic with hyperthyroidism.

Mrs. C.J.W., aged 43, in September 1929 had an infected finger. and sugar was found in her urine. Fasting blood sugar 167 mg. per 100 cc. On a diet containing 80 gm. of carbohydrate, 60 gm. of protein and 140 gm. of fat, the urine remained free from sugar without the use of insulin. In July 1932 she exhibited a nodular goiter, auricular fibrillation and a basal metabolic rate of plus 42. The fasting blood sugar was 227 mg. per hundred cc. A diagnosis of hyperthyroidism complicating diabetes mellitus was made. After hospitalization and insulin therapy the patient had a subtotal bilateral resection on October 5, 1933. The immediate postoperative course was difficult but after a few days became normal and the patient was discharged from the hospital seventeen days after operation. On October 25, 1933 the basal metabolic rate was normal and the patient free from sugar on a diet of 100 gm. of carbohydrates, 70 gm. of protein and 90 gm. of fat, plus 45 units of insulin daily. From October 1933 to date the patient's condition has been satisfactory, with normal weight, regular pulse of 78, urine free from sugar on a diet of approximately 150 gm. of carbohydrate, 70 gm. of protein and 90 gm. of fat (total calories 1690) and with an insulin dosage of 44 units daily.

In the course of our thyroid and general surgical experience, we have been impressed with three clinical associations: 1) the question of the potential diabetic—that individual with a low liver glycogen threshold; 2) the activation of the hyperglycemia into a true diabetic as the result of infection or hyperthyroidism; 3) a basic biological deficiency in certain females, to wit, obesity, fibroids, gall stones, adenoma of the thyroid and diabetes. If and when, one or more of these biological factors operate in such an individual with a basically insufficient insulin production, diabetes is the logical expectation.

In hyperthyroidism uncomplicated by diabetes the fasting sugar is normal but the body metabolism is markedly accelerated; the tempo of catabolism is increased, and the body requires an additional fuel intake. In diabetes mellitus there is a pancreatic insulin deficiency and therefore a diminished ability to catabolize a normal fuel intake. Furthermore, there is always variation from the normal in the behavior of a hyperthyroid patient to his carbohydrate metabolism. "The patient must receive carbohydrates if the function of the liver is to be supported and insulin must be taken if the carbohydrates are to be utilized."⁴ Under conditions of normal metabolism a tissue cell receives a given quantity of glucose and requires for its catabolism an adequate amount of insulin. If the tempo of metabolism is increased by an excess of thyroxin as exhibited by an elevated metabolic rate then an additional amount of insulin will be required even if the quantity of glucose is constant. The higher the basal metabolic rate the more insulin will be required. The increased cell oxidation in hyperthyroidism destroys insulin effect much more rapidly than in the non-complicated diabetes. "Hyperthyroidism exhausts the store of liver glycogen and keeps on exhausting it."⁵

The occurrence of hyperthyroidism in diabetes demands a close association between the internist and the surgeon. The hyperthyroidism is the most immediate problem and should be corrected surgically at the first opportune occasion. It is not necessary to have the urine sugar free. Indeed, many times it will be impossible to accomplish this desirable end. The treatment of the diabetic should be the concern of the internist and the surgeon should proceed to carry out the preoperative and surgical therapy for the hyperthyroidism. The preoperative treatment in surgery is exactly the same as for hyperthyroidism in the non-diabetic, and the fact that the hyperthyroidism is so eminently linked with the diabetes is under no circumstances a contra-indication to modern thyroid surgery. Experiments and experience demonstrate that hyperthyroidism is ameliorated by the administration of iodine preparations. The surgical therapy or surgical intervention should be for the purpose of carrying out an adequate resection of thyroid tissue in sufficient amount to produce a more or less semi-permanent minus basal metabolism.

The preoperative treatment of hyperthyroidism in the diabetic requires:⁶

- 1) Bed rest.
- 2) A rational diabetic diet.
- 3) An adequate amount of insulin.
- 4) Overcoming dehydration by an adequate water intake by intravenous solutions of normal saline, Ringer's solution or distilled water plus the addition of 5-10 percent dextrose.
- 5) Preoperative iodine control by Lugol's solution, 7 minims, t. i. d., in a full glass of water one hour after each meal, or adding sodium iodide, gr. xv to one of the intravenous infusions.
- 6) Preoperative sedation by paraldehyde 1 cc per ten pounds of body weight in 150 cc of starch water by rectum, one hour before operation and morphine gr. 1/6, scopolamine gr. 1/150th, one-half hour before operation.
- 7) Ethylene or general anesthesia.

Conclusions.

1) In every suspected case of diabetes and hyperthyroidism the diabetes must be established as a true diabetes. "For the present and therefore to avoid premature diabetic cures we have raised the standard for a diagnosis of diabetes in hyperthyroidism to a blood sugar of 0.15 percent fasting or 0.20 percent or more after meals in addition to glycosuria."⁷

2) Diabetes is not cured by a successful resection of the thyroid but an active destructive condition—hyperthyroidism—is eliminated.

3) The correction of hyperthyroidism, either primary as in Graves' disease, or secondary as in adenomatous goiter by adequate surgical resection of the thyroid diminishes the intensity of the co-existing diabetes and renders the diabetes more amenable to diet and insulin.

4) The hyperthyroidism in the diabetic patient differs very little from hyperthyroidism in the non-diabetic but the diabetes is intensified because the hyperthyroidism "reduces the ability of the diabetic patient to utilize carbohydrates and decreases the efficiency of the unit of insulin."⁸

5) In the presence of the two conditions, diabetes and hyperthyroidism, attack the hyperthyroidism first.

6) In a diabetic a non-toxic goiter has no influence upon the diabetes either before thyroid resection or afterward. Excess thyroxin destroys available insulin, and it is the insulin factor that determines the intensity of the diabetes.

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Dr. Smith:

The discussion of this paper will be carried on by Dr. Charles G. Child of the New York Hospital.

Dr. Child:

I think that Dr. Heyd has very fairly presented the present status of the problems involved in treating patients who present a combination of diabetes and hyperthyroidism. When I was asked to discuss his paper it became of interest to me to find out in general what had happened to these individuals in our institution during the last ten years. I found that during this period 1200 patients had been admitted with toxic goiter. In eighteen of these there was an associated diabetes. Briefly the significant details associated with these individuals are as follows:

There was one death on the second postoperative day, presumably due to coronary thrombosis. In four patients the diabetes was sufficiently mild to be controlled successfully by diet alone. In this group the one death occurred. In seven patients there was no change in the pre and postoperative dietary and insulin requirements. In six patients there was a reduction in the insulin requirements after operation. This group was somewhat difficult to evaluate for in each instance there was also a reduction in the carbohydrate intake in the postoperative period. In one patient there was a progressive increase in the insulin requirements in the year following operation at which time the insulin dose was stabilized. In studying the types of goiter encountered it was found that fifteen were adenomatous while only three were diffuse. As might well have been expected, the largest group, sixteen in all, fell between the ages of 45 and 65. There was one juvenile goiter with a severe diabetes.

From the study of these patients it has been our conclusion at the New York Hospital that the combination is not as serious as the textbooks would lead one to suspect. The dire warnings must be a hangover from the pre-insulin days when certainly these patients must have been most difficult to man-

age. The only worse situation that I can imagine must have been prior to the use of insulin and also prior to the surgical treatment of hyperthyroidism itself. In following the modern methods, however, as Dr. Heyd has outlined them, this combination of diseases may now be handled with a rather certain degree of safety.

I would perhaps differ from Dr. Heyd in a few points. First, I think we would employ local infiltration with procaine as the anesthesia of choice in these patients, for it makes the management of the diabetes far easier during the first few postoperative days. Second, I believe that it is impossible to attack either one or the other of the problems first; both must be handled together. Unless the diabetes is carefully controlled, it may be difficult to establish a preoperative gain in weight, one of the most significant criteria for when a patient is ready for operation. Third, we still feel that in the majority of patients it is unnecessary to divide the strap muscles in the course of thyroidectomy. Adequate exposure can be obtained by separating them in the midline.

One other factor was of interest, namely, that in preparing these patients for operation the time required was approximately 15 percent longer than in those uncomplicated by diabetes.

It has been a pleasure to hear Dr. Heyd's paper, and to present this discussion in the light of our experiences at the New York Hospital.

(Further discussion of Dr. Heyd's paper will be found below under remarks of Dr. Elliott P. Joslin.)

Dr. Smith:

The second paper of the evening "Preliminary Report on Amputations Below the Knee for Gangrene in the Diabetic" will be presented by Dr. Samuel Silbert of the Mt. Sinai Hospital and Montefiore Hospital.

"Amputation Below the Knee for Gangrene in the Diabetic—Preliminary Report," Samuel Silbert, M. D.

The operative mortality in thigh amputations for gangrene in the diabetic as reported in many recent papers on this subject remains appallingly high. Combining the most recent statistics of twelve representative metropolitan hospitals, a total of 637 thigh amputations were done in diabetics with 300 deaths, a mortality of 47 percent. (Table 1) I have omitted from this summary the figures published by McKittrick from the New England Deaconess Hospital of Boston as his mortality is not representative of the experience of most large general hospitals. Since the technical procedure of a thigh amputation is simple and requires no great skill, the only conclusion that can be drawn from a consideration of these figures is that this operation is too severe for the average patient with diabetes.

It is readily apparent why this is so. The patient with diabetic gangrene is usually a poor operative risk. He is past middle age, and often has complicating arteriosclerotic cardio-renal or cerebrovascular disease. His vitality may have been reduced by prolonged suffering and by absorption of toxic products from his gangrenous or infected foot. To relieve pain he has received considerable quantities of narcotic drugs. It has been difficult properly to control the diabetes because of the diminished effectiveness of insulin in the presence of infection and gangrene. Such a patient should be subjected to as little operative trauma as possible. The operative procedure should be brief, profound anesthesia should be avoided, and amputation should be carried out as far distally as possible.

It has been taught for many years that amputations should be done through the thigh in order to insure adequate circulation for healing. This widespread belief has been proven incorrect by numerous surgeons in the past few years. McKittrick, Beverly Smith, Macs, Crossman, and others have advocated amputations below the knee, and have reported good results following this procedure. My own experience likewise indicates that amputations can be performed safely below the knee in diabetic patients, even when the popliteal artery is closed and oscillometric readings indicate a serious deficient circulation.

In an effort to find the simplest and quickest operative procedure which would relieve this group of patients, I have for the past four years done mid-leg, guillotine amputations, shortening the bones, and leaving the stump wide open to heal by secondary granulation. This procedure has been carried out in all patients without selection, regardless of whether femoral



FIG. 1
Early stage of healing. Note skin drawn over end of stump, by contracting scar tissue.

or popliteal arteries have been open or closed, and whether or not infection was present. In the first few cases a tourniquet was used around the thigh to expedite the operative procedure. Three patients developed gangrene of the leg stump and required secondary thigh amputations. The use of a tourniquet was therefore abandoned. Since then over 75 consecutive cases have had mid-leg guillotine amputations without the use of a tourniquet. Healing in all these patients has been surprisingly good and in no case has a higher amputation been required. In a very few patients minimal necrosis of the skin margin has developed, but this has never interfered with a satisfactory end result.

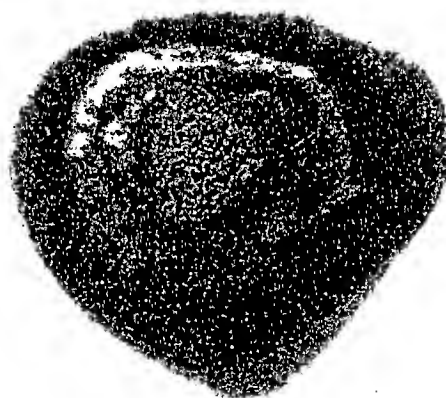


FIG. 2
Later stage of healing. Small granulating wound in center of contracting scar.

The process of healing presents some surprises. As soon as a rim of scar tissue forms at the periphery of the wound, contraction of the scar tissue begins and gradually pulls the skin down over the end of the stump (Fig. 1 and 2). This process continues until healing is complete, and the final scar is frequently so small that it can be covered with a 25 cent silver coin (Fig. 3, 4, 5). It is not necessary to apply any form of traction to the stump to accomplish this result. The pull of the contracting scar tissue is sufficient. Complete healing usually requires from 10 to 12 weeks. Patients are allowed out of bed the day after operation in most cases, and

can leave the hospital on crutches 4 to 6 weeks after operation.

Eighty-two patients with diabetes and extensive gangrene of a foot have now had amputation by this method. Many of the operations were done by members of the house staff under my supervision. A few of the cases included were patients seen in consultation and operated upon by colleagues.

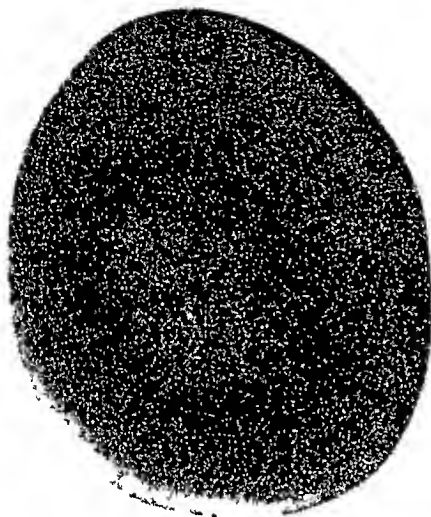


FIG. 3

Well healed stump. Note relatively small area of scar to circumference of stump.

There have been five deaths, a mortality of slightly over 6%. In addition, 12 non-diabetic patients with arteriosclerotic gangrene have been similarly treated with one death, making a total of 94 cases with 6 deaths. Forty of these have been ward patients at the Montefiore Hospital with 4 deaths. Fifty-four have been patients seen in private practice with 2 deaths. I might point out that, in general, patients admitted to the ward service at Montefiore Hospital are old and decrepit, and the hazards of operation are maximal in such a group. In an effort to evaluate the operative risk, all patients were graded as A, B, C, or D risks, depending on age, degree of coronary involvement, hypertension, toxicity due to spreading gangrene or infection, and degree of vascular impairment. Graded in this manner, only 6 of the 82 diabetic patients could be regarded as A risks, 24 as B risks, 31 were C risks and 21 were D risks. The significance of these figures is clear. It is not necessary to have a high mortality in amputations for gangrene in the diabetic. When the severity of the operation is reduced to the limited endurance of the patient, this mortality can be reduced to slightly over 6%.

Certain other advantages of the low amputation should be stressed. The use of an artificial limb is greatly facilitated if the patient retains his knee joint and about six to eight inches of his leg. Such patients are frequently able to walk without the use of a cane or crutches, and with scarcely any perceptible limp. On the contrary, when amputation is done through the thigh, experience has shown that almost none of the women and only about half of the men ever accustom themselves to the use of an artificial leg. Many of the 94 patients in my present series, including one man and one woman over 80 years of age, have been fitted with and are wearing artificial limbs. The stumps which result from the operation have stood up well under use with artificial legs. I know of no instance where a well healed stump has broken down and required further surgery.

It is worth recording that none of the below-knee stumps have been persistently painful. Pain in thigh stumps is common, and is one of the most distressing complications of amputations of the lower extremities. Every surgeon has had such patients with intractable pain who were not relieved

by injections or reoperations on the sciatic nerve or sympathetic nervous system. In a recent article published in the Journal of the American Medical Association, White discusses this unfortunate complication, and suggests that cordotomy or even excision of parts of the cerebral cortex are justified in an attempt to relieve such pain. I do not know why leg stumps are painless, but I call your attention to this great advantage of the low amputation.

A brief description of the operation may be of interest. The patient is placed on the table face down, as his position permits flexion of the leg, and makes the operation much easier. Spinal anesthesia, using less than 100 mgm. of novocaine, or light general anesthesia is employed. A tourniquet is not used. A circular incision is made through the skin and fascia at a level 8 inches below the patella. Flaps of any kind are avoided. The muscles are divided at the level of the retracted skin. As soon as the superficial layer of calf muscles is sectioned the posterior tibial vessels and nerve are exposed, lying on the deep layer of muscles. The vessels and nerve are ligated and divided and the nerve is injected with alcohol. The leg is then flexed and the anterior tibial group of muscles is sectioned, exposing the anterior tibial vessels and nerve near the interosseous membrane. These structures are then ligated and cut, thus controlling the major sources of bleeding. The leg is again placed horizontal and the deep layer of muscles on the posterior surface is sectioned. The muscles are then separated for a few inches from the bones and the bones are sawed through, the tibia about one inch and the fibula about two inches above the level of the skin incision. Periosteum and bone are cut at the same level. The anterior edge of the tibia is then beveled by an oblique saw cut. Any muscle that has been damaged during the procedure is trimmed away, and careful hemostasis obtained. The wound is thoroughly irrigated with a pitcher of sterile water. This completes the operation. The wound is left wide open and is dressed with a combination of paraffin mesh and vaseline gauze. A posterior molded plaster splint is applied and the dressing is not changed for a week. Thereafter the wound is dressed with cod liver oil ointment every 3 days until it is



FIG. 4

Characteristic small scar at end of well healed stump.

healed. There is frequently considerable secretion from the wide open wound and usually some superficial slough of damaged tissue for the first two or three weeks. Then the wound gradually becomes a clean granulating surface in the center of a rapidly contracting scar. Infections of the stump or other complications are extremely rare. The postoperative course is usually smooth and painless.

It is important to continue the use of the posterior molded splint until the wound is well on the way to healing. Con-

tracture at the knee takes place readily unless a splint is used, and such a contracture is difficult to overcome.

Are there any contra-indications to the mid-leg amputation? In my opinion there is only one group of cases that is not suitable for this procedure. These are the patients who have had a recent thrombosis of the femoral artery, and gangrene develops within a few weeks of onset. Such cases are readily

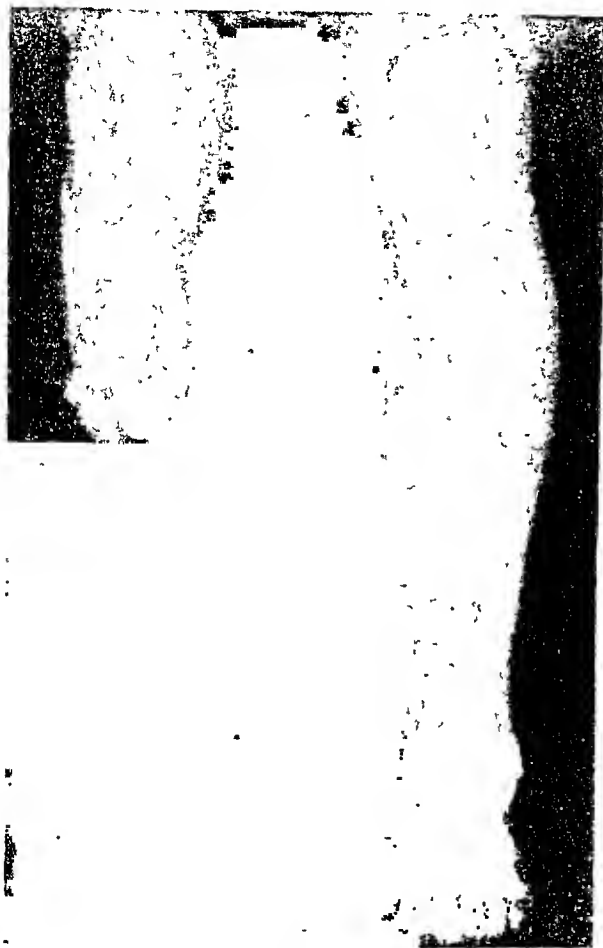


FIG. 5
Well healed stump after guillotine amputation. Preservation of knee joint and upper part of leg greatly improves ability to walk with artificial leg.

identified, as they give a history of abrupt onset of pain without preceding intermittent claudication. Unless there has been an interval of at least three months after the arterial occlusion, there has not been time for an adequate collateral circulation to develop to the mid leg, and it is not safe to amputate below the knee. It has been my experience that such cases are relatively few.

The diabetic patient with progressive gangrene of the foot, with or without infection, has a condition which threatens his life. Amputation of the part cannot be avoided. It has been gratifying to me to find that the simple operation described accomplishes this purpose with a minimal loss of life. Additional advantages are that the patient is left with a functioning knee joint and a comfortable stump.

Dr. Smith:

The discussion of this paper will be carried on by Dr. Thomas J. O'Kane of the Morrisania City Hospital.

Dr. O'Kane:

The paper we have just heard symbolizes a large forward step in the treatment of a condition which up until a comparatively few years ago was sadly neglected. A condition in which the mortality when analyzed at many large voluntary and municipal hospitals in the City of New York was

TABLE I

Mortality Following Amputations for Gangrene in the Diabetic

Hospital	Cases	Deaths	Period	% Mortality
Philadelphia General	130	73	1926-1933	56
Philadelphia Episcopal	56	27	1926-1935	48
Mary Immaculate (Jamaica)	24	12	1930-1935	50
Montefiore	17	10	1932-1936	59
Massachusetts General	36	12	1916-1926	33
Mount Sinai	68	26	1926-1936	38
Morrisania	45	27	1931-1935	60
Bellevue, 1st division	40	21	1931-1935	52
Bellevue, 2nd division	35	22	1931-1935	63
Bellevue, 3rd division	70	26	1931-1935	37
Bellevue, 4th division	24	18	1931-1935	75
Lenox Hill	13	5	1935-1939	46
St. Luke's	34	9	1934-1938	27
New York	33	9	1932-1940	27
Roosevelt	12	3	1935-1939	25
Totals	637	300		47%

appalling. Dr. Silbert cites a mortality of 47% among 637 thigh amputations. The figure is undoubtedly correct, and I know that before ten years ago it was much higher and in fact, almost double that figure. The efforts of such organizations as the New York Diabetes Association have unquestionably done much to bring about a change. Nevertheless it must be remembered, that, included in estimating this mortality are cases in the older age groups, having kidney, heart, cerebral, liver, and general damage, in whom no other operative procedure but thigh amputation was warranted. But there is no doubt that many thigh amputations were performed and are being performed unnecessarily and without regard to the proper indications for such an operation. It was with this point in view that Dr. Williams and I formulated our classification as a guide to surgery in the diseases of the extremities in diabetics and also attempted to outline a clinical method of estimating the circulatory status of the limb disregarding oscillographic and other instrumental procedures. Recognizing this, since 1932, I have used the modified guillotine amputation below the knee, as advocated by Dr. Beverly Smith, with increasing frequency.

I discarded the use of a tourniquet, not because I had seen any disastrous results from its use actually, but because I felt theoretically it may do damage and because I found it unnecessary, there being rarely any circulation in the larger vessels of these legs. This has been further confirmed by the necessary use of the tourniquet in refrigeration anesthesia which it has been my custom to use in preference to any other type of anesthesia in the past two years. I have used this type of anesthesia in well over 50 cases, and have seen no ill effects or stump gangrene that could be ascribed to the tourniquet.

Dr. Silbert's results in allowing spontaneous healing to occur following the guillotine amputation are undoubtedly good, but we feel that this is unnecessary because it prolongs hospitalization and convalescence. By means of the Smith modification of the guillotine, primary closure is effected in non-infected cases, and in infected cases secondary suture in four to seven days is practiced successfully. This is easily done. Thus shortens convalescence by ten to sixteen days to complete healing.

Our experience with the use of the artificial limb in thigh amputees coincides with that of Dr. Silbert. We often find the artificial limb relegated to the closet after a few attempts at use.

The occurrence of pain in the amputation stump is very much less in below-the-knee amputations. We found that infection in the stump is a large factor contributing to post-operative pain.

A very much larger number of below-the-knee amputa-

tions can be done in the older age group where sufficient time has elapsed to develop adequate collateral circulation. As a matter of fact, the majority of these cases have had little or no blood supply through the main vessels of their limbs for years, as is evidenced by lack of bleeding from the main vessels at operation when no tourniquet is used.

Dr. Silbert has shown that given proper and adequate diabetic care it is possible to apply thoughtful and rational surgical treatment to this problem and to remove the awful spectre from extremity surgery in diabetes.

While I may differ in detail, I agree thoroughly with Dr. Silbert. I would like to ask him a question since he did not speak of his diabetic control. What was the medical co-operation in his cases?

I wish to thank Dr. Silbert for this opportunity of hearing and discussing this excellent presentation.

Dr. Silbert:

Diabetic control is not as a rule a difficult matter in these patients since their diabetes is usually not severe. I handle the diabetic control myself in the patients I am treating privately, unless there is some unusual complication. The patients at Montefiore Hospital are taken care of by the house staff. It is best to have a sugar-free urine, and patients are given as much insulin as may be required to accomplish this result. Once the leg is off, the diabetic control becomes rather simple. Rarely is it necessary to use more than 50 units of insulin a day in these patients.

It might be pointed out that the majority of these patients have closed popliteal arteries; most surgeons would, therefore, have done thigh amputations. In my opinion, this is not a criterion for surgery above the knee.

My experience with the tourniquet is that it is very detrimental in certain cases. It promotes sloughing. An attempt has been made to evolve a procedure without its use. In most of these patients you are inviting trouble when the wound is closed. Primary union, with closed popliteal arteries, cannot be expected. I, therefore, leave these amputations open.

(Further discussion of Dr. Silbert's paper will be found below under remarks of Dr. Elliott P. Joslin).

Dr. Smith:

On behalf of the Surgical Section of the New York Diabetes Association, I want especially to thank the next speaker for coming to address us. He came on behalf of his colleague, Dr. Howard Root, who is ill and unable to be present. Dr. Elliott P. Joslin of Boston needs no introduction. He will speak on "The Medical Pre and Post Operative Treatment of Surgical Diabetics".

Dr. Joslin:

Dr. Root had a bad time of it with virus pneumonia and he was in the hospital for several weeks but he is now much better. It has been a great pleasure to come here tonight.

Discussion of Dr. Heyd's paper continued

In regard to the papers already presented, I should like to refer first to the one by Dr. Heyd on the thyroid complication. The diabetic patient with thyroid complication demands the closest cooperation between the medical man and surgeon.

I remember two cases that drove that home to me. One whom I saw about thirty-five years ago died in coma. The second patient and the one that stands out above all the others in my mind was a patient of Dr. Lahey who came in one night at about ten o'clock. That patient changed all the rules of the hospital for then no routine urinalysis was done at midnight. In the morning when the laboratory was open the patient was in diabetic coma. This is what the combination of diabetes and hyperthyroidism really means, a rapidly changing condition. Since this occasion it has been a rule of the hospital that a urinalysis be done on every patient coming in regardless of the time of admission. Lahey and his group have formulated a principle which holds with all of the surgeons and us, that is, the surgeon does just what he wants to for the patient; it is our job to keep the patient from the diabetic standpoint alive. We have never, and I can

honestly say that, gotten into any trouble about orders because we have things so arranged that the surgeon writes down what orders he wants and they are carried out. We never change their orders; there is the closest cooperation among us.

I see Dr. Mosenthal in the audience and I should like to ask him about his experiences with hyperthyroidism — do these patients have less arteriosclerosis than other people? I should like to see some statistics on this because my feeling is that people with hyperthyroidism generally have very good arteries. I believe this is true and I wish there might be more said about it.

We see a great many simple adenomas in our diabetics. Many patients with adenoma do not have any hyperthyroidism but I do feel that unless there is something definitely against it, these adenomas should come out. My opinion on that goes back to one of the Mayos who pointed out the occasional cancer of the thyroid developing in an adenomatous gland. This is a terrible thing to see. I do think we should take advantage of good surgery and attack these adenomata of thyroid more frequently than is commonly done. I agree thoroughly with all that Dr. Heyd has said.

During 1942 and 1943 thirty-four operations on the thyroid gland were performed by the Lahey Clinic on our patients with no mortality. Preceding the operation the diet has been one high in carbohydrate and calories, particularly if hyperthyroidism either primary or secondary to adenoma has been present. Prior to operation it is the rule for patients with hyperthyroidism to remain in bed four days and then gradually to get up and about until operation on the tenth day. Lugol's solution is prescribed after the first metabolism test and until the day of operation. The second metabolism test is done on the seventh day. Phenobarbital, grains $1\frac{1}{2}$, is given on the night before operation, and if the patient has been toxic, $\frac{1}{4}$ or $\frac{1}{2}$ grain is given three times a day previous to operation.

Thiouracil is still in an experimental stage. A paper from the Lahey Clinic is appearing shortly in the Journal of the American Medical Association but Dr. Lahey emphasized at our staff meeting that it is not without danger and is thus in marked contrast to the use of Lugol's solution. I may add that our group see such good results from the management of thyroid cases by the Lahey Clinic that we never institute treatment without a consultation with them.

Patients with simple adenomas may be in the hospital only one or two days before the operation is performed.

Recently, concealed or latent hyperthyroidism has been discovered in a considerable number of our diabetic patients who failed to do well. In these patients careful studies disclosed the hyperthyroidism, and its cure by operative measures has led to extraordinarily good results. I cannot emphasize too strongly the idea that if a diabetic patient does not improve by methods which should bring this about, one must invariably hunt for a complication such as hyperthyroidism.

Discussion of Dr. Silbert's paper continued

The surgical status of the patient rules, and the surgeon decides when to operate. The task of the physician is to keep the patient alive and to adapt treatment to the surgical emergency. How well Dr. Silbert has recorded the wonderful improvement for operations on the lower extremities and, in particular, has shown how small the mortality may be for amputation below the knee when intimate correlation exists between the surgeon and internist! Especially deserving of attention is the circumstance that these operations were not always done by him but by a group working along the same lines. I feel that his low mortality in comparison with the previously high mortality in a group of scattered hospitals in various cities should not be interpreted as evidence to favor amputation below the knee for safety's sake, but rather should be taken as evidence of good surgery under the careful direction of one surgeon who is particularly interested in diabetes, rather than surgery performed by a group of surgeons, excellent though they may be, who are without special interest and experience in diabetes.

Major amputations at the New England Deaconess Hospital numbering 767 between 1932 through 1942 showed a mortality of 12.3 percent, but major amputations for the three years 1941, 1942, and 1943, numbering 132, were performed with 5 deaths, a mortality of 3.8 percent. In the beginning these amputations were under the supervision of Dr. Daniel Fiske Jones, but for many years have been under that of Dr. Leland S. McKittrick and a group of his associates.

I should like to ask Dr. Silbert to watch his cases and note how many ultimately will have to have the other leg off. Of 100 of our major amputations, 39 at a later time had to have amputation of the other leg.

With regard to surgery in obstetrics, Dr. Priscilla White will soon make a formal report. To the 125 diabetic pregnancies and deliveries already reported by Dr. White, she now has added 51 more cases, making a total of 176 patients whom she has followed through the greater part of the course of their pregnancies. I think one of the secrets of the success obtained is due to the fact that there has been the same doctor, obstetrician, anesthetist, pediatrician, and, in fact, supervising nurse. The series includes 52 normal cases with 50 living babies; 89 abnormal cases treated with hormones and under careful supervision with 81 living babies; and 35 abnormal cases untreated or poorly treated with 17 living babies, making a total of 176 cases with 28 deaths. The fetal mortality—16 percent.

In general, the diet throughout the pregnancies varied from carbohydrate 180, protein 90, fat in variable amounts, to carbohydrate 200 and protein 120. Salt was restricted after six months. In the management of these pregnant women one always must remember their tendency to renal glycosuria and to acetoneuria, the latter in my experience, particularly if the carbohydrate falls under 100 grams daily. One does not attempt to get these patients sugar-free with insulin.

Crystalline insulin and protamine zinc insulin have been administered before breakfast, and almost invariably additional doses of crystalline insulin later in the day. Insulin is given 24 hours before a surgical delivery but no additional later during the day before or on the morning of delivery. After delivery, the insulin has been resumed up to or less than the usual dose of crystalline and protamine zinc insulins. Tests of the urine are also made at 11:30 a.m. and 4:30 p.m. and 8 units of crystalline insulin added if red, orange or yellow test with Benedict's solution. One is careful to exclude a test of urine first voided after intravenous glucose.

1000 cc. of 5 percent glucose in water is given intravenously starting before and continued during operation, and 1000 cc. of 5 percent glucose in saline some hours postoperatively. The carbohydrate up to 100 to 200 grams in all, including that intravenously, is given as hot liquids, tea with sugar, malted milk with water, and gradually one works back to the regular preoperative diet.

No preoperative medication was given. Spinal anesthesia was employed, but the dose was smaller than the usual dose and always with ephedrine. Oxygen is given to the patient during cesarean section for sake of the baby. Pantopon is injected as soon as the baby is delivered. Emphasis is put on giving no preoperative medication.

Remember one is dealing with a potentially atelelectatic baby. Extra care, therefore, is necessary for the infant with special effort made to see that the child is drained, suctioned, and mechanically stimulated, often every hour. Many of the babies during pregnancy are exposed to extra fluids (hydramnios). The rule has been for the baby to be put into the incubator for 24 hours routinely, and especially so lately because of the shortage of nurses. The mature appearance of the baby should not deceive the doctor. The infant should be treated with as much as or greater care than a premature infant.

I should like to present something a bit new in our group and I brought a statement with me which I think is thoroughly applicable to the operation below the knee. This was written by Dr. Francis D. Moore who is with McKittrick and Pratt

and who was the first one from Boston to be decorated for operating at Guadalcanal. This statement which deals with "*Experiences with Penicillin in Diabetic Gangrene*" I shall read.

"When a virulent infection increases the local metabolic requirements of tissues in an arteriosclerotic limb and decreases the blood supply by edema and venous thrombosis, a situation arises in which the loss of the part from gangrene may result. It is in this group of cases that penicillin may conceivably make its greatest contribution: namely, in those patients with an absent dorsalis pedis pulsation or with poor collateral circulation, who, prior to the onset of infection, have maintained a fairly adequate extremity, in whom a virulent invasive infection has severely embarrassed the local blood supply. In such cases an effective anti-bacterial substance might control the infection and again allow the circulation to be adequate for the limb."

"Our experience now comprises the use of penicillin in seven patients. In five of these penicillin has been administered to control infection, and a local surgical procedure has been successfully carried out, rather than resorting to the low thigh amputation which would have been necessary under previously accepted methods of treatment."

"The results thus far have been satisfactory. Using penicillin, it is possible to control local infection, and if penicillin is used locally as well as systemically, the wound may be sterilized. We have not yet found much alteration in the wound flora if the drug is only administered systemically."

"Using penicillin, the open wound of drainage or of metatarsal amputation appears to granulate much more rapidly and much more cleanly than under previous methods of treatment, allowing the usage of multiple pinpoint grafts to close the operative defect. This later method has been used in several cases and the unsuccessful 'takes' of the pinpoint grafts have been quite unusual for a pulseless foot."

"In order to reduce the circulatory factors in the distal part of the foot to a minimum, a procedure is being developed in which a transmetatarsal amputation is carried out, removing the entire distal part of the foot, and leaving the proximal portion which has more adequate arterial supply. Penicillin has been applied locally and systemically, and as soon as the wounds granulate, multiple grafts are placed, and the wound is thus closed."

"Our experience with this group of cases under penicillin treatment is still very limited and the transmetatarsal amputation has only been used in two cases."

"It is much too soon to report any definitive results, but it is safe to say that this extremely effective antibacterial agent may come to occupy a place of importance in the treatment of diabetic gangrene."

Pre-Operative Treatment. It is preferable to have the diabetes controlled, but no delay should ensue in case of an emergency. Thus in several instances acidosis and appendicitis have co-existed, but the time of the operation has seldom been delayed over six hours. As a matter of fact, usually in most cases the diabetes is quite well controlled before operation unless fulminating infection exists such as a carbuncle, and even then surgical preoperative treatment for a few days allows for the treatment of the diabetes. However, I still remember a standard saying of Daniel Fiske Jones that if the patient cannot survive the hazard of going to bed for twenty-four hours, the chances of a successful surgical operation in that period are dubious. Naturally this would not hold in a case of active appendicitis.

At 6:00 p.m. of the preoperative day surgical patients receive a soap suds enema even though the operation is quite trifling. They have a routine supper, but coarse vegetables are avoided. At least for five hours before operation the patient receives nothing by mouth, and I have noticed that this period has been lengthened often to twelve hours. Recently several patients have received Nembutal and some, morphine one and a half hours and one hour respectively before operation, but as a rule most patients receive no preoperative medica-

tion at all because of the danger of inducing vomiting—20 percent of patients will vomit as result of morphine alone.

Insulin is withheld on the morning of operation until the patient returns to the ward. Thereafter, the customary dosage is administered, and later in the day before noon, before night, and in the late evening, additional crystalline insulin is

given according to the formula

R	Y	G
8	4	0

Post-Operative Treatment. The minimum carbohydrate during the first twenty-four hours after operation is about 100 grams. Usually 1000 cc. of 5 percent glucose in saline is given intravenously on return to the ward, and in case the patient cannot begin to take simple liquids, a second 1000 cc. of 5 percent glucose in distilled water is administered. In operations on the gastro-intestinal tract vitamins are given intravenously with the glucose or saline.

The regular preoperative diet is gradually resumed, and all of us have felt that if the patient is kept without food for a considerable period prior to operation, the diet can be increased much more rapidly than when the patient has received even such simple liquids as orange juice or ginger ale five hours before the time of operation.

Insulin nearly always can be reduced within a few days after the operative procedure. No attempt is made to keep the patient sugar-free for the first one or two days because so frequently glucose is given parenterally. Never expect to get the patient sugar-free right after an operation. The nurses are instructed not to give insulin by the fraction formula described above on the first urinary test following intravenous medication. Even if the patient became sugar-free after a few days, insulin is maintained in small doses when the fasting blood sugar is 140 mg. or more, or the blood sugar after food exceeds 170 mg. In many instances, patients can omit insulin, but these are dangerous cases because, as my son has taught me, if the patients do not prick themselves each morning, they are apt to forget they have diabetes. We often say that the diabetic who omits insulin causes us more worries than the diabetic who consistently takes a small dose, even 8 or 10 units.

Following operation patients especially with major amputations are turned on the side every two hours. Rubber sheets are avoided; Balkan frames are invariably used so that the patient can move about by himself, and a narrow pillow is placed under the ankle of the sound foot, so that the recovering patient in moving about the bed will not injure the heel.

Routine rounds in every surgical case demand 1) examination for bed-sores, which seldom nowadays are encountered; 2) recognition of the possibility of an impaction; 3) search for a distended bladder; and 4) critical clinical observation of the physical status of the patient and his blood and urine to differentiate between the possibility of an insulin reaction and surgical shock.

Anesthesia. Spinal anesthesia has been the almost invariable rule in nearly all major amputations.

Sulfadiazine has been administered prophylactically (when time allows) for two to three days before the operative procedure. The first dose would be 2 grams followed by one gram every four hours. It is rare, however, that more than six grams have been given for more than one day; subsequently, the usual dose is four grams. Alkalies have not been given with the sulfadiazine, and we have depended on the laboratory levels for sulfadiazine, on care that the urinary output reaches 1200, preferably 1500 cc. in twenty-four hours. Observations are made on the state of kidney function. Repeatedly this past year the question has arisen as to whether we should use alkalies as a routine, but we feel our results have fully justified our avoidance of this additional medication.

I always enjoy coming down to New York and I shall not soon forget about the 94 cases as reported by Dr. Silbert.

Dr. Smith:

The discussion of Dr. Joslin's presentation will be opened by Dr. Edward Tolstoi of New York Hospital.

Dr. Tolstoi:

I think all of you will agree with me that Dr. Joslin's sketely presentation is more stimulating, more erudite, and more choekful of experience than another man's deliberated presentation. However, as interesting and stimulating as his remarks were to me personally, I experienced a feeling of embarrassment, because it was my lot to discuss the paper on the program entitled "The Medical Pre and Postoperative Treatment of Surgical Diabetics." Naturally, I assumed that Dr. Joslin would devote most of his time to that thesis. Some of his remarks were pertinent, but most consisted of comments on the other papers which have been read this evening. I am, therefore, somewhat in the position of the young student who most carefully learned the names of the twelve apostles for his final examination. He was told that it would be the only question. When he appeared at the examination, much to his dismay, he was asked to differentiate between the major and minor prophets. This was quite a blow, but he recovered and wrote, "Far be it from me in my humble capacity to differentiate between such great men, but the list of the twelve apostles is as follows." Profiting from his experience I will, therefore, tell you my ideas about the diabetic patient requiring surgery.

Number one, hydration is very important. The patient must be wet before the operation. Number two, glycogenation—the liver must be rich in glycogen.

The patient must be given ample fluid, with a substance which will bind it. Salt is ideal. Preoperatively, I recommend one gram of salt in tablet form, every two hours, followed by a glass of water. This may be started twenty-four hours preoperatively. The patient need not be disturbed at night. Fluid may also be given as saline by elysis or intravenously, the former for the patient over sixty or anyone suspected of cardiac insufficiency, the latter for the young patient.

Now as to the second principle that of glycogenation. The only efficacious means of enriching the liver glycogen in a diabetic patient is by means of carbohydrate and insulin. The patient may be given a 5% glucose solution simultaneously with the saline and about 25 units of regular insulin. This permits a coverage of one unit of insulin for each two grams of glucose. The amount of the fluid administered at any one time is 1000 cc. and this should be repeated as needed.

Food is withheld the morning of the operation and the fasting preoperative blood sugar is not done, as I feel it is not very helpful.

The control of the post operative glycosuria is not emphasized, as it has been my experience that wounds healed by primary union even though the patient reveals a glycosuria of as much as 70 to 100 grams in 24 hours.

When we have a patient whom we expect to be under anesthesia for a long time, we insert a mushroom retention catheter and connect it to a receptacle at the bed so that we can draw off urine for analysis every two hours. The urine is then examined for sugar and acetone and the insulin requirements adjusted accordingly. It is more prudent to keep the insulin a little below actual needs rather than run the hazard of hypoglycemia.

Dr. Joslin mentioned that he likes to keep salt low. That is at variance with our concept, and I would appreciate if he would elucidate a little more.

I find that the surgical diabetic presents no great problem. The general principles of preparation are the same as in any other patient, and now that insulin is available, ketosis is not too great a hazard.

Thank you. I am grateful for this opportunity to discuss.

Dr. Smith:

The discussion will be continued by Dr. Louis Bauman of the Presbyterian Hospital.

Dr. Bauman:

Hyperthyroidism complicated by diabetes:

Surgeons favor a high carbohydrate diet during the preoperative period of toxic goiter; when diabetes is associated, a large amount of insulin may be necessary to control carbohydrate metabolism. After operation when the caloric requirement has decreased, regulation is easier at first.

I was impressed by the ameliorating effect of partial thyroidectomy on the severity of the diabetes, but later experience did not always confirm this early impression.

The treatment of diabetes complicated by surgical conditions.

During ordinary existence it is possible and desirable to obtain accurate regulation of the diabetes but this is rarely possible during infectious or immediately following a surgical operation.

On the day of operation, per oral feeding is interdicted. Usually a clysis of 1500 cc. of 5 per cent glucose in saline is given and this is preceded by about 15-20 units of uncombined insulin. If possible, the urine is tested every two hours thereafter and the dosage of insulin graded to the excretion of sugar (i.e., 10 units for 4+ or 3+, 5 units for 2+ or 1+ glucose). If the urine specimen is not obtained, a finger blood sugar will be of even greater value, for in older people hyper-

moval of sequestra, she recovered and left the hospital a week ago.

The table includes some of the diabetic data.

It is evident from the table that the severity of the diabetes varied from day to day and this was due to the variable absorption from the infected focus. The relatively good control, though, on a diet of over 3,000 calories was obtained by a morning dose of 15 units of protamine and 65 units of globin insulin.

Dr. Smith:

The discussion will be continued by Dr. George E. Anderson of the Brooklyn Hospital.

Dr. Anderson:

It has been a great pleasure for me to be here this evening. It is always stimulating to hear a paper by Dr. Joslin, and

Date 1944	C	Diet grams P	F	Blood Sugar mg %		Standard	Insulin units	
				11.30 a.m.	4.30 p.m.		Protamine	Globin
1/4	150	100	25	408	301	22		
1/5	"	"	"	312	306	35		25
1/6	"	"	"			30		35
1/7	"	"	"	346	140	30		30
1/10	"	"	"	135	107	35	15	55
1/11	200	100	80	123	192	5	15	60
1/19	"	"	"	69	61		15	60
1/20	"	"	"	155	73		10	55
1/24	225	100	125	305	161		10	55
1/26	"	"	"	108	62		15	75
2/5	275	100	150					
2/16	275	100	175	216	127		5	50
3/8	"	"	"	306	157		10	60
3/13	"	"	"	63	60		15	65
3/29	"	"	"	76	48		15	65
4/4	"	"	"	125	68		15	65
4/5	"	"	"	404	444		15	65
4/6	"	"	"	285	67		15	65

glycemia may exist without glycosuria. We have recently seen a typical diabetic retinitis in an elderly man without glycosuria but with hyperglycemia. As soon as possible, fluids are given by mouth, and later the previous diet and insulin are resumed.

The diabetic is extraordinarily sensitive to the products absorbed from wounds on infected areas. The dramatic lessening of the severity of the diabetes after amputation of an infected foot is a good illustration.

The following slide illustrates the preoperative treatment of severe acidosis occurring in a diabetic man of sixty with a large carbuncle of the neck.

Time	Fluids Given I.V. cc. PO	Carbony grams	Sugar	Urine Diabetic	Blood Sugar	CO ₂	Insulin Units	Sid Carb grams
Feb. 15								
4:00 p.m.	1000		4+	0	.46	14	50	3
6:00 p.m.			4+	4+			50	3
8:00 p.m.	1000		4+	4+				3
9:00 p.m.			4+	4+		19.5	20	
11:00 p.m.			4+	4+				
12:00 Mid								
Feb. 16								
1:00 a.m.		100	3+	0				
4:00 a.m.		100	+	2+			20	
7:00 a.m.						31		
8:00 a.m.	1000		0	0	.085	36		3
12:40 p.m.		200	0	0	.151		15	
1:30 p.m.	1000							Operation

The treatment consisted in the administration of salt solution, insulin and moderate amounts of sodium bicarbonate rather than sugar.

The next slide is a record of the progress of a girl of fourteen who had diabetes for eleven years and was transferred from another hospital where she had been for two months for osteomyelitis of the lower half of the femur, staphylococcus aureus septicemia, pericarditis, and pneumonia. She had received about 1,200,000 units of penicillin during this time and regular insulin to control the diabetes. The osteomyelitis of the femur dominated the picture when she entered the Presbyterian Hospital where she remained for about four months. Three senior surgeons favored amputation at the hip joint but with the help of large doses of penicillin, drainage, and re-

this evening's has been no exception. I am in the same quandary as Dr. Tolstoi. There is possibly some excuse for "ad-libing" and I shall proceed.

I feel we might attempt to find common denominators which are applicable to all surgical diabetes. One of these is the age of the patient. Prima facie, the diabetic of eight or ten years' duration must be considered, so far as his cardiovascular system is concerned, to be ten years older than his chronologic age. Thus, the man of 58 years, by virtue of his diabetes, is really 68 years of age from the standpoint of surgical risk. He cannot be expected to withstand the "wear and tear" of surgical shock as would a younger person. He must be prepared for

his ordeal with this in the mind of the medical attendant, and this leads to a second common denominator which is pertinent to all diabetics facing surgery. Ordinarily, the diabetic lacks facility in polymerizing liver glycogen. This mechanism can be further embarrassed by faulty dietary prescription and insulin administration.

I like to think of the liver as a glycogen reserve, not in a pool sense as the gall bladder for bile, but rather in the nature of a commercial bank where the assets are represented by a dynamic balance between intake and output.

Glycogenic and glycogenolytic processes are constantly going on, and simultaneously. The urgent need is to attain a temporary over-balance of formation over breakdown of glycogen during the preoperative and the critical operative and

postoperative periods.

It is well known that a large dose of insulin in the non-diabetic will result in glycogen breakdown. A small or optimal dose of insulin in the diabetic favors liver glycogenation, but even in the diabetic, an excessive dose of insulin will cause glycogen breakdown and an abnormal carbohydrate mechanism. Witness the lack of sugar control after an episode of insulin shock, possibly as result of the compensatory suprarenal response. If you send the surgical patient to the operating room at a time when he is on the verge of insulin shock, what can you expect of him when he adds to this surgical shock?

In the Brooklyn Hospital, it is our habit to withhold insulin on the morning of surgery, at least, regular or crystalline insulin. It may be feasible to give 50% of the usual potassium zinc insulin for its postoperative effect. We reduce P.Z.I. on the day before operation, so that this insulin effect will not "catch the patient" on the table. We depend in the main on rapidly acting insulins postoperatively in frequent small doses.

Secondly, it has been shown by Cori and others that the liver glycogenizes better from a high blood-sugar level than from a low. It is, therefore, our policy to keep blood-sugar in the surgical candidate at the highest level which is consistent with negative or reasonably small output of urinary sugar. Under these circumstances, we worry very little about the glycosuria provided obligatory fat metabolism is avoided. An attempt is made to keep blood-sugar somewhere near the threshold level or slightly above.

In the Brooklyn Hospital, the patient receives his usual supper on the night before surgery; before retiring, he is given 8 oz. of milk and four crackers (about 32 gms. Cho.) for nascent glycogen formation thru the night. In the morning, on awakening, he is given 8 oz. of orange juice (24 gms. of glucose in rapidly available form). During surgery, the patient receives from 25 to 50 grams of glucose intravenously and slowly throughout this period. Postoperatively, we aim to supply from 100 to 200 grams of glucose in 24 hours by whatever route is most feasible.

The essential point from the internist's angle is to glycogenize by adequate preoperative carbohydrate prescription and cautious judicious use of insulin. Too often, as we have learned from sad experience, shock on the table or delayed shock is attributed to the surgical procedure rather than being placed in the internist's lap where it belongs. The quest for textbook normal blood-sugar and urine may have dire conse-

quences. On the other hand, insulin properly administered has made of the surgical diabetic, a relatively normal surgical risk.

I wish to take this opportunity to thank the Surgical Committee for a very fine meeting and to express our thanks to the speakers of the evening.

Dr. Smith:

I should like to call on Dr. Mosenthal to comment on Dr. Joslin's question about hyperthyroidism and arteriosclerosis.

Dr. Mosenthal:

Most of the hyperthyroid cases are rather on the younger side before you really expect them to have arteriosclerosis. Another side of the story that may be of interest is that arteriosclerosis is often benefited by small doses of thyroid even though the arteriosclerotic does not exhibit the slightest sign of hypothyroidism. Old age, among other things, manifests a deficiency in thyroid and so you ease them along. The arteriosclerosis that occurs with too little thyroid is just a general sign of degeneration that comes with advancing years thru all the organs of the body.

Dr. Smith:

I should like to call on Dr. Joslin for any closing remarks he might wish to make.

Dr. Joslin:

I am glad that Dr. Tolstoi brought up the point of having these patients protected from dehydration. I think the idea of giving some patients salt solution before operation is often desirable (if they don't exhibit albumen, high blood pressure and edema). I would like to emphasize that we must be careful with these patients for if one gives them too much intravenously, they get so much salt that it might be more than you would want. The idea of giving some of them salt before the operation is good.

How are blood transfusions handled here in New York? So many of these patients get many blood transfusions—sometimes four or five. We are trying now to get these patients who come to the hospital to bring their own donors and it thus doesn't cost them anything. We feel that when the patient is brought in and it is expected that an operation is to be done, the friends or relatives who brought the patient in should give blood. When people come to the hospital from a long way off, we are going to try to see if we can't get their local blood banks to give us some blood.

Dr. Smith:

I wish to thank the speakers for their participation this evening. This meeting is now adjourned.

Dietary Factors in the Treatment of Cirrhosis Without Jaundice

By

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IN RECENT years the results of treatment for cirrhosis of the liver have become more promising. This is due mainly to a better understanding of the underlying disturbed physiologic and pathologic processes. Up to a few years ago cirrhosis of the liver was considered an intoxication, alcohol being most often considered the offending agent. Animal experiments and clinical observations in recent years, however, seem to indicate that liver cirrhosis is a deficiency disease.

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Various studies point to a deficiency of some unknown fraction of the vitamin B complex as the cause of hepatic cirrhosis in experimental animals. ^{1, 2, 3, 4} Gyorgy and Goldblatt,⁵ on the basis of a large number of experiments, believe that a deficient intake of protein brought on by the anorexia of vitamin B deficiency, is the actual cause of the cirrhosis in experimental animals. The protein deficiency, with its attendant lack of lipotropic amino acids which are necessary for the fat turnover in the liver, leads to increased fat deposition. Of the lipotropic amino acids methionine is the most important one. If methionine is not present in the food it may be formed in the body if sufficient labile

methyl groups are available. Such methyl groups can be provided by choline. In the opinion of Gyorgy and Goldblatt, therefore, the protein deficiency leads to fatty livers and later cirrhosis. Production of fatty livers by other means has also led to cirrhosis formation.^{6, 7} Fatty livers were also produced by a high fat diet with alcohol.⁸ Several investigators produced cirrhosis in animals by a diet rich in fat and poor in protein.^{9, 10, 11, 12, 13, 14} Some consider a diet high in cystine as an important cause of cirrhosis.^{15, 16} The production of experimental cirrhosis in animals has been associated with attempts to prevent or cure it by the administration of choline or methionine.^{17, 18, 19, 11}

In view of the above discussed experimental findings the role of alcohol in the development of hepatic cirrhosis became doubtful. At present, alcoholism is considered a condition which interferes with proper nutrition and thus brings about the deficiency. Evidence

arrest of the cirrhotic process was noted. Broun and Muether found marked clinical improvement in their cases of cirrhosis following choline administration.³⁰ The lipotropic effect of protein upon human cirrhotic livers is further indicated by the reduction of the fat and increase of the protein concentration in the liver when parenteral amino acids are administered.³¹

Because of the foregoing findings it seemed important to investigate the effects of a diet rich in protein and carbohydrates and low in fat, supplemented by choline and vitamin B complex on the course of human cirrhosis. Since some evidence exists, mainly derived from animal experiments, that the extractives of meat have a harmful effect upon the liver,³² the protein given was of lacto-vegetarian sources only.

The evaluation of therapeutic results in human cirrhosis is rather difficult, although changes in the clinical course might be used as indices of improvement

Table 1.
Solid (Meat Free) Diet

	Amount	Pro- teins	Fats	Carbo- hydrates		Amount	Pro- teins	Fats	Carbo- hydrates
Breakfast					2:00 P. M.				
9% Fruit	200 Gm	2	-	18	Brewer's Yeast	25 Gm	12	-	10
Cooked cereal	200 "	4	2	16	Milk	100 "	3	4	5
Sugar	10 "	-	-	10					
Toast	40 "	4	-	21	3:00 P. M.				
Butter	10 "	-	9	-	Dietene	50 "	16	-	28
Eggs	1 "	6	6	-	Milk	150 "	5	6	8
Coffee	10 "	-	-	-	Crackers	2 "	1	1	5
Sugar	200 "	-	-	10	Lecithin	15 "	-	-	-
Milk	100 "	6	8	10	Supper				
9:00 A. M.					3% Vegetable	100 "	2	-	3
Milk	100 "	3	4	5	6% Vegetable	100 "	2	-	6
Brewer's Yeast	25 "	12	-	10	18% Vegetable	100 "	3	-	18
					9% Fruit	200 "	2	-	18
Egg	1 "	6	6	-	Sugar	20 "	-	-	20
3% Vegetable	100 "	2	-	3	Bread	30 "	3	-	16
6% Vegetable	100 "	2	-	6	Butter	6 "	-	5	-
18% Vegetable	100 "	3	-	18	Milk	200 "	6	8	10
Bread	30 "	3	-	16					
Butter	6 "	-	5	-	8:00 P. M.				
12% Fruit	150 "	3	-	18	Dietene	50 "	16	-	20
Sugar	20 "	-	-	20	Milk	150 "	5	6	8
Milk	200 "	6	8	10	Crackers	2 "	1	1	5
Jello	100 "	3	-	22	Lecithin	15 "	-	-	-
					Total Proteins 141; Fats 79; Carbohydrates 401.				
					Total Calories 2879				

100 Gm. or more of carbohydrates are given as a 10% (or higher) dextrose solution intravenously

exists, however, that in the presence of a deficient diet, alcohol increases the severity of the liver cirrhosis.⁵

Beneficial effects of yeast as a source of vitamin B upon liver cirrhosis²⁰ have been claimed, but have not been substantiated.²¹ The therapeutic effect of methionine is due not only to its lipotropic effect, but also apparently to some direct effect upon the damaged liver by providing necessary enzyme systems.^{22, 23} The beneficial effects of protein in the prevention of cirrhosis is apparent from various experiments which have revealed the protecting effect of protein against hepatic damage.^{24, 25, 26}

Additional evidence that human cirrhosis of the liver is a deficiency disease is found in the fact that in countries where nutritional deficiencies are common there is a high incidence of cirrhosis^{27, 28, 29} even in children. Post and Patak³³ have reported very encouraging results from their attempts to treat human cirrhosis with a highly nutritious diet generously supplemented with the vitamin B complex. Besides an increased survival time and general improvement, evidence of an

or failure. Since changes in the clinical picture, however, are very slow, it was thought advisable to investigate whether changes in the liver function tests or in the hematological findings could be used as an index since these changes might occur in a shorter time than those in the clinical picture. Since in cases with acute hepatitis, as indicated by the presence of jaundice, possibilities for a spontaneous improvement exist, it was also thought important to select cases in which no evidence of an acute liver damage existed. It was expected that the effect of therapy would be best followed if cirrhotic patients without jaundice were treated for limited periods of time and the influence of the treatment upon liver function tests and hematological conditions determined at short intervals. The short interval would, in addition, make it fairly certain that changes observed could be attributed to the therapy. In the selection of the various liver tests, special emphasis was placed on changes of the plasma protein, especially of the albumin level which has been considered a valuable index in the evaluation of liver cirrhosis.³³ In the

evaluation of hematological conditions special emphasis was put upon the occurrence of "target" cells, cells which we consider to be of great significance in liver damage.

MATERIAL AND METHOD

Ten patients with liver cirrhosis were selected for the study and on these the following liver function tests were performed: The oral hippuric acid excretion test, the cholesterol/cholesterol ester partition, quantitative urinary and stool urobilinogen excretion, icterus index, non-protein nitrogen determination, determination of albumin-globulin ratio, the cephalin cholesterol flocculation test and the Takata-Ara reaction. The hematological work-up consisted of erythrocyte, leucocyte, platelet and reticulocyte counts; hemoglobin, hematocrit and sedimentation rate determinations; differential counts and examination of the red cells in the smear preparations. In a number of cases marrow examination was also performed. After one week the tests were repeated, and if almost identical results were obtained, the patients were given a diet containing 6 gram carbohydrate, 2 gram meat free protein, and 1 gram fat, per kilogram. The average diet contained over 3,000 calories daily. In the administration of vitamin B supplements, care was taken that enough preparation would be provided which contained all members of the B complex. Yeast was therefore given, and injections of crude liver extract were administered. Choline was administered as lecithin, either in the form of a spread on crackers or in cookies. For additional supplement of other vitamins and minerals, dietene* was given in form of a milk mixture. Table 1 shows the diet used in these patients. An attempt was made to keep the patient in the hospital as long as possible or until definite clinical and laboratory improvement was noted. At weekly intervals the liver function tests and the hematological observations were repeated. After dismissal from the hospital, the patients continued on the above diet and returned at monthly intervals for checkup.

RESULTS

The re-examination of these patients showed that following four weeks of medication comparatively little change was noted. However, when the patients were on the diet for a longer time, i.e., six weeks up to sixteen weeks, there were definite manifestations of improvement both subjectively and objectively.

In two of the ten patients the ascites and edema were unchanged at the end of the observation period (4 and 5 weeks, respectively); in four the ascites and edema were decreased after the observation period varying from 6 to 16 weeks; and in the remaining four the ascites and edema had disappeared at the end of the observation period (6 to 16 weeks). The total protein increased appreciably in six cases. The albumin fraction increased in five; the globulin fraction in five. In two cases there was a decrease in the albumin and in four there was a decrease in the globulin. The percentage of cholesterol esters increased in 6 cases. The hippuric acid excretion increased in only four cases.

*Dietene—generously supplied by the Dietene Co., Minneapolis, Minn.

Table 2.

Clinical and Laboratory findings in 14 patients of cirrhosis without jaundice while under observation from 1 to 4 months; 10 patients receiving a special diet with high vitamin supplements and 1 being used as controls.

Name	Weeks under observation	Total protein		Albumin		Globulin		Percentage of cholesterol esters		Hippuric acid excretion	Takata-Ara reaction	Cephalin cholesterol flocculation test	Hematologic picture	Urinary urobilinogen	Improvement	
		before	after	before	after	before	after	before	after						Subjective	Objective
N. S.	4	7.0	7.3	4.9	2.6	2.0	4.7	6.9	51	0.9	1.0	—	unchanged	no significant changes	unchanged	unchanged
E. J.	8	6.9	7.6	2.6	2.7	4.3	4.9	28	26	1.3	1.7	unchanged	unchanged	no significant changes	moderate	some
W. K.	6	4.0	7.0	2.6	1.4	3.3	3.6	39	73	1.2	1.4	unchanged	unchanged	no significant changes	marked	moderate
J. N.	4	7.0	7.0	3.5	4.0	3.5	3.0	53	84	3.5	3.5	unchanged	improved	no significant changes	marked	moderate
T. P.	16	5.7	5.5	3.0	4.0	2.7	1.5	81	70	2.5	2.6	unchanged	—	no significant changes	moderate	moderate
E. P.	8	4.4	5.4	2.9	2.9	1.5	2.5	31	63	1.4	2.4	unchanged	—	no significant changes	marked	marked
J. S. P.	16	5.0	8.7	2.6	5.5	2.4	3.2	41	95	1.7	3.7	unchanged	unchanged	no significant changes	marked	marked
S. V.	5	7.6	9.0	2.3	4.7	5.3	4.3	32	60	3.1	3.8	unchanged	improved	no significant changes	marked	marked
F. W.	4	8.0	7.0	3.1	3.3	4.9	3.7	45	33	2.0	2.1	unchanged	unchanged	no significant changes	slight improvement	slight improvement
E. Z.	6	7.3	8.5	3.8	4.2	3.5	4.3	55	56	2.6	3.6	unchanged	improved	no significant changes	moderate	moderate
F. D. W.	20	7.2	5.3	4.3	3.8	2.9	2.0	51	50	—	2.1	—	—	no significant changes	unchanged	unchanged
P. K.	4	6.4	7.6	3.2	4.7	3.2	2.9	71	73	2.4	2.8	—	deceased	no significant changes	unchanged	unchanged
D. S.	4	5.8	7.6	2.6	3.6	3.2	4.0	59	—	2.3	2.0	—	deceased	no significant changes	worse	died
E. P.	4	6.6	4.7	3.2	3.5	3.4	1.2	42	47	2.4	2.5	—	—	no significant changes	unchanged	unchanged

The Takata-Ara and cephalin-cholesterol flocculation test remained unchanged in the cases which otherwise showed improvement.

The hematologic picture showed improvement in only three cases. Subjectively, marked improvement was found in four cases, some improvement in five, and one case appeared unchanged.

Four similar patients were used as controls on the routine diets. In three of them there was no change while one showed an increase in the ascites and edema. The total protein decreased in two and slightly increased in the other two. The cephalin flocculation decreased in two and increased in one with one remaining unchanged. The globulin fraction decreased in all four; the cholesterol to esters ratio in 1 case. The hippuric acid excretion decreased in one, increased in one, and remained the same in two. Clinically, three cases remained the same while one died.

DISCUSSION

As seen from the data presented, a definite improvement in the liver function tests was obtained in a number of patients. The restitution of the plasma protein level was much slower than improvement in other liver function tests. This may be explained in part by the fact that the hypo-proteinemia present in these conditions is an index of a general protein deficiency of the

tissues. Studies of Sachar³⁴ *et al* have shown that of 30 grams of protein administered, only one goes into the blood while the rest goes into the tissues. It appears, therefore, that it is necessary first to replete the tissue protein before a recognizable rise in the plasma protein occurs. The changes in the clinical picture appeared rather late and are best explained as a result of the improved liver conditions as indicated by the results of the liver function tests. The hematological findings did not change at all during the observation period. This fact is of great significance because it may throw some light upon the nature of the hematological changes.

SUMMARY AND CONCLUSION

1. Patients having cirrhosis with jaundice improved subjectively and objectively as measured by the results of liver function tests on a dietary regimen with added high vitamin supplements.

2. Restitution of the plasma protein levels and change in the A/G ratio appear usually late in the course of treatment.

3. The Takata-Ara reaction and the cephalin-cholesterol flocculation remain unchanged even when other symptoms show marked improvement.

4. The hematologic picture, except for improvement in anemia, does not show any changes commensurate with the subjective improvement.

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Studies of Gastric Secretion During Electro Shock Therapy

by

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IN ORDER to study changes in gastric secretion as a result of electric shock therapy for psychotic patients,¹ the patients swallowed a small Rehfuß tube previous to treatment. No food had been ingested for twelve hours preceding the investigation. The fasting gastric juice was withdrawn, the quantity noted, and it was analyzed for free and total acid. Convulsive therapy, as described in a previous paper,² was administered with the tube in place, and the stomach contents withdrawn during the fit and for a time thereafter. The succeeding samples were analyzed in the same way as the fasting gastric juice.

Nineteen patients were studied. Fourteen patients had fasting gastric juice low in quantity and acidity. Two of these patients had complete achlorhydria. These two also had other hyperthyroid symptoms so the lack of acid may have been due to an overactive thyroid. Of these patients with low fasting acidity, nine showed a rise in gastric acidity during or shortly following the induced convulsion.

The following protocol, illustrative of the above results, is given.

II is a report on one of the patients whose condition was uncomplicated by hyperthyroidism.

Case II shows the quantity and acidity of gastric juice aspirated before, during, and after a convulsion. The acidity is given in cc of one tenth Normal NaOH calculated to titrate 100 cc gastric contents.

In the five remaining patients, all of whom were diagnosed as schizophrenics, the fasting gastric juice was high in acidity during each trial. After electric shock therapy there was no significant change in the gastric juice. Two of the patients showed low gastric acidity in the fasting juice on certain occasions. After electric shock treatment the acidity increased. On other trials the fasting gastric juice showed considerable acid, and no increase in acidity followed the convulsive treatment. The following protocol Case III shows the results from this latter type of patient.

Case III shows the quantity and acidity of gastric juice aspirated before, during, and after a convulsion. The acidity is given in cc of one tenth Normal NaOH calculated to titrate 100 cc gastric contents.

CASE I

Trial I

Before Treatment			During Grand Mal			10 minutes After Grand Mal			20 Minutes After Grand Mal		
quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid
25 cc	0	8	5 cc	0	8	40 cc	20	27	15 cc	18	34

Trial II

10 cc	0	12		20 cc	20	34		6 cc	18	36		8 cc	15	15
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The above table shows the quantity of gastric juice and the acidity before, during, and after a convulsion. The acidity in cc of tenth normal NaOH calculated to titrate 100 cc gastric contents.

The gastric juice of five of the fourteen patients with low fasting acidity showed little or no change in acidity following electric shock therapy. These five patients included the two who were mentioned above as having hyperthyroid symptoms. The following protocol Case

In the majority of these cases showing low fasting gastric acidity, electro therapy induced changes which indicate vagus activity. In those cases where the fasting gastric juice was highly acid, no change was induced by electric stimulation of the brain. Presumably the vagus was active previous to treatment and further stimulation brought no increase in activity. Previous investigation^{3, 4, 6} on cardio vascular reactions have led Krinsky and Gottlieb⁶ and Hoskins and Jellinek⁷

CASE II

Trial I

Before Treatment			During Grand Mal			10 minutes After Grand Mal			20 minutes After Grand Mal		
quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid
35 cc	0	9	15 cc	0	4	17 cc	0	9	5 cc	0	10

Trial II

35 cc	0	15		25 cc	0	6		28 cc	0	10		5 cc	0	12
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Submitted April 7, 1944.
From the Department of Research of the New York Psychiatric Institute, Dr. E. S. Barrera, Chairman.

to regard the schizophrenic as having reduced sympathetic activity. Studies on blood sugar changes in

CASE III

Trial I

Before Treatment			During Grand Mal			10 minutes After Grand Mal			10 minutes After Grand Mal		
quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid	quant.	free acid	total acid
10 cc	0	2	30 cc	11	17	90 cc	29	30			
Trial II											
25 cc	23	36	35 cc	21	38	8 cc	38	38	40 cc	14	30
Trial III											
90 cc	13	17	25 cc	18	23						

schizophrenics also indicate increased vagus activity.^{5,9,10} The five cases in which we report abnormally high gastric acidity in the fasting gastric juice con-

firms this overactivity of the parasympathetic nervous system in this disease, and suggests further study of autonomic balance in psychoses.

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Effect of Electric Shock Therapy on Muscle Movements

by

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THE following studies were undertaken in order to observe the muscle movements which occur as a result of stimulation caused by the electric shocks which are administered for treatment of various psychotic conditions. The types of motility and secretion indicate the part of the brain which has been predominantly stimulated as a result of the therapy.

Electric shock therapy, as introduced by Cerletti and Bini,¹ involves the use of an alternating current which produces unconsciousness in the patients. The electrodes are applied on both temples; the current is applied for approximately one tenth of a second; the voltage is usually about eighty. Just how much resistance the current encounters in going through the head is not accurately determined, but the above conditions produce a grand mal seizure with phases which appear to be identical with those of a true epileptic fit.

Tonic generalized contractions are followed by a clonic phase. Marked cyanosis of the face occurs.

The stopping of the heart action and cyanosis of the face during the fit indicate vagus stimulation. The presence of bile in the gastric juice after a shock also suggests vagal activity consequent upon stimulation of the medulla. Heilbrun and Weil² report hemorrhage in the capillaries and small veins of rabbits and rats given electric shock treatment simulating the treatment of patients with functional psychoses. They interpret the cause of these hemorrhages as due to powerful contractions of the ventricles following cessation of the electric stimulation with reestablishment of the arterial flow encountering resistance of the venous side of circulation with stasis of blood in the lungs. The latter condition was indicated by cessation of respiration which returned several seconds after the termination of the shock. The sudden increase in venous pressure led to rupture of the thin walls of the smaller veins. This

explanation indicates that vagus stimulation is the ultimate cause of the hemorrhages.

Kessler and Gelhorn³ report a marked hyperglycemia in normal rats and a fall in blood sugar in adrenalectomized animals after convulsive seizures induced by electric currents. These effects are mediated by the sympathetico-adrenal and vago insulin systems, respectively since no change in blood sugar occurs in adrenalectomized vagotomized animals under these conditions. That the vago insulin system is excited by the electrically induced convulsions in the normal animal is shown by the fact that when the vagi are sectioned below the diaphragm the hyperglycemic effect produced by the sympathetico adrenal system is greater than when impulses may also reach the islets of Langerhans via the vagi.

Records were made of the movements of the stomach by means of the technique described by Carlson.⁴ The patient, who had no food for the preceding twelve hours, swallowed a Rehfuß tube to which a balloon was tied. The free end of the tube was attached to a recording tambour and the system was filled with air. Pressure changes in the stomach during convulsions were recorded on revolving paper. At the same time, a pneumograph was placed over some of the striated muscles to record their action during the convulsion. Usually the pneumograph was put over the abdominal muscles in order to show whether or not their activity might be responsible for the pressure changes which occurred in the stomach. Fifteen patients were studied for this type of muscle activity. On some of the patients several records of gastric activity could be obtained. On most of the individuals, only one or two records were taken.

In all cases in which the patient went into grand mal attacks, a rise in intragastric pressure was recorded immediately following the application of shock. The rise in pressure lasted a varying number of seconds and then fell off. In seven of our cases this was followed by a second rise in pressure.

The rise in pressure above the basal level usually lasted during the clonic phase. The pressure was above the basal level (that intragastric pressure prior to the induction of shock) for thirty to forty seconds. When the second rise in pressure occurred, it followed the clonic phase and its average duration was thirteen seconds. There was considerable variation in the time of the second contraction, the extremes being from seven to forty-eight seconds.

During the recording of the changes in intragastric pressure the record from the pneumograph over the abdominal muscles showed no sustained changes, although the twitches were recorded. When the fit was over and breathing resumed, the lever attached to the

pneumograph recorded the breathing motions, and changes in intragastric pressure were recorded simultaneously with breathing motions. Since the two recording levers did not move synchronously during the fit, we may assume that the recorded changes in intragastric pressure were due to contraction of the gastric musculature. This would be due presumably to stimulation of the vagus nerve during application of the shock.

It could be argued however, that the recorded pressure changes in the stomach might be due to contraction of the diaphragm although these changes were shown not to be synchronous with the movements of other striated muscle. Five records were taken of gastric pressure changes during petit mal seizures. During such seizures there are no convulsive movements of striated muscle. In three such recordings, increase of pressure in the stomach was shown following induction of the shock. In two cases little or no changes in pressure were observed. These results then give further evidence that the gastric musculature itself contracts and, that the changes in pressure are due to this contraction.

Records from striated muscles during electrical shock were taken from arm, leg, or abdomen simultaneously with the gastric records. A corrugated rubber tube was placed on the desired region and connected with a rubber tube to a Marey's tambour for registration on a kymograph. It is interesting to note that after shock, a tonic stage of variable duration occurs, followed by rapid clonic contractions. The initial rate is often between 8-14 per second. In former studies, one of us⁵ pointed out that this corresponds to the rhythmical discharge rate of the cerebral cortex. Later the rate slows up and finally contractions occur every second, or every two seconds. The meaning of this slowing up procedure is not yet clear. Lowenbach and Lyman⁶ explained it in their animal experiments, as due to cortical fatigue. Further experiments will be necessary to clarify this phenomenon.

The rise in gastric pressure coincides with the tonic and rapid rated clonic contractions in the striated muscles. During the slowing down of the rate the gastric level of pressure decreases and contractions of the abdominal walls or diaphragm are transferred to the balloon in the stomach.

CONCLUSION

Gastric contraction occurs during the initial stage of the effect of electric shock on striated muscles. Sometimes there is a second similar effect following the initial contraction of the stomach. We are apparently dealing with the effect of vagal stimulation occurring during discharge in the brain cortex, following application of electric shock.

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Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

TEMPLETON, F. E., AND MOORE, P. M.: *Cardiospasm and the normal esophagus: a roentgenologic study of muscular action.* (Proceed. Central Soc. Clin. Research, v. 16, p. 7, Nov. 1943.)

Both normal individuals and patients exhibiting cardiospasm were used in this roentgenologic study. The subject was placed prone or supine so as to eliminate the effects of gravity on deglutition.

In the normal subject three types of muscular activity were shown by the esophagus. A primary wave, which was part of the act of deglutition, began at the pharynx and travelled down the esophagus. This wave forced the bolus along. A secondary wave, not part of the act of swallowing, began in the region of the aortic arch and progressed along the lower half of the esophagus in a manner similar to the primary wave. Finally, tertiary waves were noted; these were localized contractions which were not peristaltic in nature.

In patients with cardiospasm the primary wave did not reach the stomach but tended to fade out in the region of the suprasternal notch. The lower esophagus showed peculiar segmental contractions which were unrelated in nature. These appeared at different levels and were insufficient in force to drive the bolus along. Tonic contractions were often present and forced the barium into the stomach. Amylnitrite relaxed all muscular activity.—M. H. F. Friedman.

BOWEL

HANNO, H. A., AND MERSH, M.: *Leiomyoma of the jejunum: intermittent melena of fourteen years' duration, and fatal hemorrhage.* (Ann. Surg., v. 120, p. 198, Aug., 1944.)

Leiomyoma of the small bowel is uncommon and occurs with equal frequency in both sexes. The site of commonest occurrence is the ileum, next the jejunum, while the duodenum is rarely affected. Most of the leiomyomata appear in the subserosa, fewer in the submucosa. The incidence of malignant change is high. Metastases of the submucosal variety have not been reported. The two chief clinical characteristics are intestinal obstruction and enterorrhagia. Roentgenologic examination frequently fails to reveal the tumor, perhaps chiefly because it occurs subseral and fails to produce a silhouette of the barium-filled small bowel. The case history is presented of a 53 year old man who for 14 years had twenty episodes of melena. The last

hemorrhage was fatal. It was felt that if a tumor had been suspected earlier, the patient might have been benefited by surgery. The authors recommend a close look-out for tumors of the small intestine.—I. M. Theone.

HERNSTONE, S. T., AND FREUND, S.: *The normal distribution of the small intestine.* (Am. J. Roentgenol., v. 52, p. 46, July, 1944.)

The study was carried out on 55 human cadavera. Intestinal segments and loops were noted to fall into definite pattern groups. However, no one group predominated.—N. M. Short.

REED, W. C., AND STORK, U. F. D.: *The retrocecal appendix.* (J. Indiana State Med. Assoc., August, 1944.)

In nine per cent of the cases the human appendix is situated behind the cecum. Inflammation of the retrocecal appendix presents certain difficulties in arriving at the diagnoses. The patient does not show signs of being ill early in the course of the disease. As in typical appendicitis, the patient experiences abdominal discomfort, anorexia and nausea but the symptoms do not focus on McBurney's area. Temperature may be normal or even below normal. Pain, if present, is not colicky but dull. Gastrointestinal symptoms may be absent. Rectal examination yields negative findings. Hematuria and pus in the urine are often present. The most important symptom is pain referred to the back, urinary bladder or external genitalia. Tenderness and rigidity seldom extend superiorly to the costovertebral angle but are confined to posterior points. The most frequent complication is subphrenic abscess which may be shown roentgenographically by an elevation of the diaphragm. The subphrenic abscess may be accompanied by signs of sepsis.—J. Cox.

BOWEL

ERB, W. H., AND SMITH, D. C.: *Atresia of the small intestine.* (Ann. Surg., v. 120, p. 66, 1944.)

Diagnosis of this relatively uncommon condition is aided by recognition of persistent vomiting and the absence of keratinized epithelium in the miconium of the new born babe. Distension may or may not be present. The plain roentgenogram of the abdomen shows the usual signs of obstruction. Atresia of the small intestine is usually easy to differentiate from the two most nearly similar conditions, atresia of the esophagus and the

rectum. A report of two cases is given. One of these represents the second known case to have recovered from operative correction of multiple atresia of the small bowel. An open side to side iso-peristaltic anastomosis was performed. The authors stress the importance of adequate pre- and post-operative control of electrolytic, protein and prothrombin levels.—Wm. Snape.

McCORMICK, N. A.: *Cancer of the rectum. (Radiology, v. 42, p. 531, 1944.)*

The author expresses optimism in discussing the question of cure in cancer of the rectum. He believes the disease is particularly amenable to cure. The early symptoms and ease with which the site of the growth may be approached, the lateness in onset of metastases, and the removability of involved lymph nodes make for a greater likelihood of cure if radical operation is performed. The 5-year survival rate is higher than with most other forms of malignant growth. In the experience of the author and his associates during the past eight years, permanent abdominal colostomies following abdomino-perineal resections are highly preferred. The patients are able to carry on useful and unrestricted lives and little difficulty is experienced by the patient in the management of the colostomy.

During the eight year period under review, 83 cases of cancer of the rectum were treated, representing 5 per cent of all cancer cases treated. Males predominated by about 33 per cent. The age range was 34 to 94 years, average age being 60 years.

The first symptoms usually shown were diarrhea (26 cases), bleeding (19 cases), constipation (nine cases), pain (six cases), loss in weight (four cases) tenesmus (three cases), cramps (two cases), piles (one case) and pruritus (one case). About seven months elapsed between onset of the first symptoms and the time a physician was consulted. Growth mass was palpable in 90 per cent of the cases. The procedures for digital examination of the rectum are outlined. Sigmoidoscopy was found particularly valuable. The palliative treatment of choice is roentgen irradiation; radium irradiation is not considered important. Surgery is the only treatment for cure but should be preceded by X-ray therapy.—I. M. Theone.

DEARING, W. H., BERKMAN, J. M., WAUGH, J. M., AND PUGH, D. G.: *Partial intermittent intestinal obstruction caused by an enterolith in the ileum. (Proc. Staff Meet. Mayo Clinic, v. 19, p. 436, Aug. 23, 1944.)*

The mechanism of formation of true enteroliths is unknown. With the following exceptions, true enteroliths are rare: ingestion of foreign materials, gallstones introduced into the intestines, medicinal concretions, appendiceal concretions, calculi formed in intestinal diverticula and fecal impactions in the large intestine.

A case report is presented of a 75-year-old physician who for 20 years experienced gaseous indigestion after meals. An examination 15 years previous disclosed no abnormalities other than achlorhydria. He showed slow but progressive weight loss. Examination revealed relatively loud intermittent peristaltic

sounds preceded by and associated with cramp-like abdominal pain. Roentgenographic study revealed an enterolith in the ileum which caused partial obstruction and marked dilatation of the ileum. Laboratory tests were normal. A hard calculus weighing 70 grams was found at operation. For 2 feet above the mass, the small intestine was markedly hypertrophied and distended. The patient's recovery was uneventful.—F. X. Chockley.

PANCREAS

MENTEN, L., AND MIDDLETON, T. O.: *Cystic fibrosis of the pancreas: report of 18 proved cases. (Amer. J. Dis. Child., v. 67, p. 355, 1944.)*

Clinically, cystic fibrosis of the pancreas is manifested by wasting, vomiting, diarrhea or constipation, bulky fatty intestinal contents, protuberant abdomen, cough and terminal pneumonia.

A report of 18 proved cases was made. Laboratory details were too scanty for evaluations. Roentgenograms showed enlargement of hilar shadows, decreasing to periphery. Pathologically the pancreas showed diffuse fibrosis with reduction in the number of acini, the epithelium of which was flattened. The liver usually showed fatty infiltration with central necrosis. The lungs showed gross bronchopneumonia: the usual bacterium found was staphylococcus aureus. The etiology is questionable.—Wm. Snape.

CUSTER, M. D. JR., AND WAUGH, J. M.: *Annular pancreas with secondary dilatation of the duodenum: report of a case. (Proc. Staff Meet. Mayo Clinic, v. 19, p. 388, July 26, 1944.)*

Only 49 cases of annular pancreas have been reported in the scientific literature. The ventral anlage of the pancreas develops independently and fails to fuse with the dorsal anlage. The ventral anlage surrounds the descending duodenum and may form a constricting band. In some cases there have been no symptoms, while in other cases there have been epigastric pain and vomiting suggesting duodenal obstruction.

A 74-year-old farmer complained of irregular and episodic dyspepsia during the past 5 years. In the last 6 months the condition became worse and the patient lost from 20 to 25 pounds. Three weeks prior to his admission to the Clinic, the patient reported that a profound weakness developed followed by a recurrent obstructive vomiting on several days. An exploratory operation was performed. Findings were a subacute ulcer of the stomach and great dilatation of the upper gastro-intestinal tract. Further exploration disclosed an obstructing band of pancreatic tissue completely surrounding the descending duodenum. Surgical procedure consisted of gastrectomy, removal of the upper 8 cm. of dilated duodenum and a Balfour-Polya anastomosis. The patient's recovery was uneventful. This is believed to be the first such case in which gastric resection was performed.—F. X. Chockley.

LIVER AND GALLBLADDER

McLEOD, K. W.: *An epidemic of common infectious jaundice. (J. Pediat., v. 24, p. 454, April, 1944.)*

An outbreak of common infectious jaundice was studied in an institution for the feeble minded over a period of thirteen months. From this study and studies reported in the literature the author noted that fall and winter were peak months in the incidence of the disease and that the age group 10 to 24 years appeared the most susceptible. The incubation period is believed to be about one month. The disease is a contact infection and is probably not conveyed by droplet infection. The duration of the jaundice varied but a prodromal stage of malaise preceded the jaundice for a period of several days. Galactose tolerance tests showed impaired liver function even one year after the acute stage had passed. No one organism was isolated from stools or bile drainage which could be designated the etiologic agent.—G. Klemmer.

WHITE, F. W.: *Methods of diagnosis of jaundice.* (New England J. Med., v. 230, p. 334, 1944).

Since cases of jaundice usually are not emergency cases, the author advocates a brief period of observation before treatment. This is based on the belief that the nature of the course of jaundice aids the diagnosis. Liver function tests should be made. Hepatocellular damage is usually responsible for a short course of jaundice with great reduction in liver function. Acute severe jaundice with brown stools is nearly always due to hepatocellular damage. Acute hepatitis and complete external biliary obstruction both give the same icterus index. Liver size is not of much aid in establishing diagnosis. Obstructive duct tumor is shown by complete absence of bile from stools. Cases of complete obstruction due to tumor never improve. The spleen is not palpable in liver tumors but is in liver cirrhosis. Hippuric acid and bromsulphalein tests are of no differential value. Tests for diastase in urine are valuable in diagnosing acute pancreatitis with jaundice.—I. M. Theone.

THERAPEUTICS

HEMMELE, G.: *Resorption of iron in pernicious anemia.* (Helvetica Medica Acta, v. 10, p. 23, April, 1943).

In patients with pernicious anemia the iron content of the serum was found elevated. This was attributed to two principle factors: the increased hemolysis and the decreased iron requirements by bone marrow due to impaired maturation of erythrocytes.

During liver treatment the conditions were improved with the result that serum iron decreased. The iron depots of the body were insufficient to meet the increased demands for erythrocytic maturation. Consequently it was necessary to give iron supplements. The intestinal absorption of iron by the patients was found to be less than in normal people, presumably because of atrophy of the intestinal mucosa.—D. A. Wocker.

GILL, A. M.: *Ulcerative colitis, clinical experiments with pig's intestine.* (Lancet, v. 246, p. 536, 1944).

A severe and chronic case of idiopathic ulcerative colitis was restored to health when taking uncooked

pig's small intestine by mouth without any other form of treatment. When the treatment was stopped a relapse followed which was overcome by further treatment. Three of 5 other cases observed over short periods seem to have derived benefit from the treatment.—Biological Abstract.

BOWEL

ROSENBLATT, M. S.: *Blood in the stools of infants and children.* (Northwest Med., V. 43, P. 78, 1944.)

Blood in the stools of infants may appear for any one of several reasons; but the commonest cause for the small amounts of bright red blood is rectal bleeding from an oral fissure. Blood from the intestine arises most frequently from intussusception and from Meckel's diverticulum. Chronic obstruction usually does not cause much bleeding and the blood in stools in cases of strangulated hernia is small in amount. Blood in the stool has been encountered in cases of regional enteritis, ulcerative colitis, and polyps of the colon.

Histories of cases encountered by the author are presented to illustrate the various causes for bloody stool, and the treatments that were attempted for each are given.—G. Klemmer.

LIVER AND GALL BLADDER

FISCHER, H., PLEININGER, H., AND WEISSBARTH, O. *The composition of bilirubin and bilirubinoid dyes.* (Hoppe-Seyler's Zeitschr. Physiol. Chem., V. 268, P. 197, 1941.)

To obtain information concerning the structure of the unsaturated side chains of ring I and IV of bilirubin, 0.3 grams of bilirubin dimethyl ester was fused with 8-10 grams of resorcinol, and vinylneoxanthobilirubinic acid ester, m. 186 degrees, obtained. Since this compound was derived from the first half of the bilirubin molecule, the structure of that half of the molecule was proved. Bilirubin was esterified with diazomethane and monomethoxy and dimethoxybilirubinic dimethyl ester isolated. However, the hydroxy groups may not have been present in bilirubin originally. Similar compounds were formed by the action of diazomethane or mesobilirubin and koprobilirubin. The azo dye hydrochlorides of methoxyneoxanthobilirubinic acid methyl ester and of the iso compound were prepared and from their properties it was concluded that the constitution of bilirubin may be unsymmetrical. A "nitrite compound", shown to be methylvinylmaleamide, was prepared from bilirubin and biliverdin in 1.5 per cent yield, and from vinylneoxanthobilirubinic acid in 6.6 per cent yield. From the above results, it was concluded that the formula for bilirubin can not contain a hydrofuran ring. It was concluded that 2 vinyl groups were present in bilirubin and biliverdin. Methods of preparation and the properties of many compounds which are considered in reference to the structure of bilirubin are given.—A. B. McCoord.—Courtesy Biological Abstracts.

ESOPHAGUS

Woodward, F. D.: *Carcinoma of the esophagus*. (*South Med. J.*, v. 36, p. 590, Aug. 1943).

The pertinent facts relative to carcinoma of the esophagus are pointed out. Most of them occur in men in the 4th and 5th decades. It is four or five times more frequent in men than in women, and occurs most frequently in the lower third in men and in the upper third in women. The majority are squamous cell in origin. When adenocarcinoma occurs, it is found in the lower and upper portions since these are the gland-bearing portions. A not infrequent complication is tracheobronchial fistula. Metastases occur in 25-50%. A fairly early sign is dysphagia. When persistent, it must be regarded with suspicion. Bleeding may be present early if there is ulceration. Pain is usually substernal, but may be in the back. The diagnosis is made in the majority of cases by X-rays. Esophagoscopy is also of value, especially for obtaining specimens for biopsy. Radiotherapy and implantation of radium or radon have not been of much value as a means of therapy. Surgical removal and reconstruction of the esophagus offer most hope in these cases.

H. N. Metzger.

SURGERY

CHILES, G. C. AND LENHARDT, H. F.: *Autoplastic sutures in repair of inguinal hernia*. (*United States Naval Med. Bull.*, v. 43, p. 83, July, 1944).

The operative technic for repair of inguinal hernia by means of autoplastic sutures is described. Fascial sutures are resistant to infection and are neither absorbed nor easily torn. The various layers of the abdomen must be carefully separated and properly identified so as to facilitate the operative procedure. The stress is distributed over the whole fascial suture strip rather than the terminal end alone. The type of repair to be used is best determined by the pathologic condition encountered.—F. N. Chockley.

WIPERT, T. B. AND MILLER, J. M.: *Surgical aspects of pancreatic fistula*. (*Ann. Surg.*, v. 120, p. 52, 1944).

Three patients with pancreatic fistulas were studied. The importance of dehydration, electrolytic imbalance (particularly base depletion) and anemia was demonstrated by the spontaneous closure of the fistula in two cases, when these factors were controlled. Atropine, ephedrine and epinephrine were found to diminish the volume of secretion. An ingenious device for protecting the skin against irritation was provided and is described. The third case required surgical interference after a trial of conservative methods.—Wm. Snape.

EXPERIMENTAL MEDICINE
SECRETION

BABKIN, B. P., AND KAMAROV, S. A.: *The effect of secretin on the concentration of pepsin in gastric juice*. (*Rev. Canadienne Biol.*, v. 3, p. 344, July, 1944).

In 1940 Pratt in England announced that secretin stimulated the secretion of pepsin by the gastric glands. In this paper Babkin and Kamarov demonstrate that the pepsinogenic effect of the secretin was due to some

substance extracted from intestinal mucosa other than the one which stimulates the pancreas. Using various preparations of secretin they found no correlation between the potency to stimulate pancreatic secretion and potency to stimulate pepsin secretion. Crystalline secretin was found to be devoid of pepsinogenic effect. Altho these workers separated the pancreatic principle from the pepsinogenic principle, they have not yet been able to isolate the latter.—M. H. F. Friedman.

CICARDO, V. H.: *Potassium release through excited mucosa*. (*Rev. Soc. Argentina Biol.*, v. 19, p. 271, 1943).

Excitation of the gastric mucosa in the dog by histamine or vagus nerve stimulation produces a noticeable decrease in its potassium concentration, as high as thirty per cent. The decrease is somewhat less during the digestion period, probably because of the restitution of the liberated potassium by ions coming from the food. Excitation of the dog's nasal mucosa by intravenous administration of pilocarpin also induces a fifteen per cent loss of its potassium concentration. Mucous membranes having higher potassium concentration before excitation takes place, show greater diminution. Elimination of potassium is believed to be due to the splitting of an organic potassium compound by the chemical substances injected, or set free by nerve stimulation; this would determine the formation of potassium ions, which, it is assumed, are given off to the exterior. The mobilization of potassium ions could be considered as the activity index of the mucosae, and as the causative agent of the secretion.—Courtesy Biological Abstracts.

MOTILITY

GOLDEN, R. F., AND MANN, F. C.: *The effects of drugs used in anesthesiology on the tone and motility of the small intestine: an experimental study*. (*Anesthesiology*, v. 4, p. 577, 1943).

Using trained chronic dogs with fistulas of the intestine as well as intestinal loops, Golden and Mann studied the effects of a large number of anesthetics on the motor activities of the intestine. With the exception of spinal anesthetics, all had either no effect or a depressant effect on the tone and motility; none had excitatory effects. Spinal anesthetics increased intestinal motor activity but only as long as the anesthesia was maintained. In the case of sodium pentothol given by vein, the rate of administration was an important factor in the amount of depression of intestinal activity it produced. Morphine had a two-fold effect. At first it produced a transitory increase in intestinal activity. This was later followed by a state of depression which was more extensive than that produced by any other of the anesthetic agents studied. In general the depth of anesthesia was more significant than the length of anesthesia in producing a condition of decreased intestinal motility.—M. H. F. Friedman.

HENSCHEL, A., TAYLOR, H. L., AND KEYS, A.: *The gastric emptying time of man at high and normal en-*

environmental temperatures. (*Am. J. Physiol.*, v. 141, p. 205, April, 1944).

Examinations of gastric emptying time were carried out on seventeen men, ages 18 to 28 years, who were kept at rest. None showed gastro-intestinal symptoms. The test meal was a mixture of oatmeal, sugar and barium. Tests were carried out with the men in an environmental temperature of 77°F, then 120°F and then again 77°F. The humidity was 50 per cent saturation and kept the same thruout the experiment. In sixteen of the subjects gastric emptying was faster at the higher temperature, the emptying time in 12 being decreased by 30 per cent. In an additional 100 men at hard work at 120°F, there were no signs of either lowered appetite or decreased gastric activity.—M. H. F. Friedman.

HADARY, G., SOMMER, H. H., AND GRANCH, J.: *The relationship between curd tension and gastric emptying time of milk in children.* (*J. Dairy Sci.*, v. 26, p. 259, 1943).

Seven normal children were fed various types of milks (fresh milk, evaporated milk, or chocolate homogenized milk) and their stomach evacuation time followed by roentgenograms. No correlation was found between the curd tension and the stomach emptying time. Contrary to some claims, the homogenized milk did not leave the stomach sooner than the fresh milk.—N. M. Short.

FETTER, D.: *The effect of electric shock therapy on gastric contraction and gastric secretion.* (*Federation Proceed.*, v. 3, p. 9, March, 1944).

Fifteen psychotic patients were studied during the process of receiving electric shock therapy. Intragastric pressures were recorded by the balloon method while abdominal muscle contractions were recorded by means of a pneumograph. Immediately following passage of the electric current thru the head there occurred a rise in intragastric pressure of 30 to 40 seconds duration. Usually a second rise of pressure followed the first, lasting 7 to 48 seconds.

In nine out of fourteen patients there occurred a rise in both free acid concentration (average 0 to 25 units) and total acid concentration (average 5 to 40 units) following induction of a grand mal attack by the electric shock. In five other patients there was no significant change in gastric acidity. The author concludes that the increased gastric motor activity and secretion were due to activation of the vagus nerve as a result of the therapy.—E. R. Feaver.

PATTERSON, T. L., AND SANDWEISS, D. J.: *The distension pressure of urine in the bladder as it influences human gastric motility.* (*Federation Proceed.*, v. 3, p. 36, March, 1944).

The subject of this study was a young woman with a permanent gastric fistula. The motility of the fasting stomach was recorded by the balloon method. When the subject retained her urine to the extent where bladder distension aroused the desire to micturate there

occurred definite alterations in the pattern of gastric hunger contractions. These became less regular and showed fluctuations in tone. As the bladder distension increased the extent of gastric inhibition increased. Finally when bladder distension reached the point where pain was experienced the inhibition of gastric motility became complete. Following evacuation of the bladder the gastric contractions resumed their normal character within a few minutes.—E. R. Feaver.

PHARMACOLOGY

HAZLTON, L. W., AND TALBERT, K. D.: *Further studies on cathartic action in mice: senna, alve, cascara, bile salt.* (*J. Amer. Pharmacut. Assoc., Scientific Edit.*, v. 33, p. 170, June, 1944).

The choleretic activity and the cathartic activity of bile salts are not related. There is no correlation between the surface activity of a drug and its ability to produce catharsis.—M. H. F. Friedman.

COLLIER, H. B., AND MACK, G. E.: *Vitamin B and phenothiazine anemia in dogs.* (*Canadian J. Research, Sec. E*, v. 22, p. 1, Feb., 1944).

Phenothiazine has been used as an anthelmintic in man but sometimes there appears an acute haemolytic anemia. Since experimental indole anemia in dogs has been found to be intensified by vitamin B deficiency, the present authors investigated the relationship between the B complex and phenothiazine anemia.

In phenothiazine anemia the hemoglobin, red cell count and hematocrit all decrease in parallel fashion. Fragility precedes and accompanies the anemia. In dogs on a vitamin B deficient diet the fragility was not affected. Reticulocytosis was stimulated by adequate amounts of the B complex and inhibited by a deficiency. Probably the B complex has no direct relation to the rate of red cell destruction but it does maintain rapid erythrocyte regeneration. The authors therefore recommended that large doses of the vitamin B complex should be administered in drug anemias.—F. E. St George.

PICK, E. P., BROOKS, G. W., AND UNNA, K.: *Inhibitory effect of sulfonamides on the action of nicotine in the isolated intestine.* (*J. Pharmacol. Exper. Therap.*, v. 81, p. 133, 1944).

Using the isolated intestine of guinea pigs and rabbits, the authors found that the effects of nicotine were inhibited by sulfonamides. Sulfathiazole, sulfamerazine and sulfanilamide were found more effective in their inhibitory action than sulfadiazine. The inhibitory effect of sulfonamides upon the action of nicotine was not antagonized by para-amino-benzoic acid. The sulfonamides did not influence the action on the isolated intestine of barium chloride, adrenaline, acetylcholine, prostigmine or histamine. The sulfonamides did not prevent nicotine intoxication in frogs or antagonize the nicotine action on the striated muscle of the frog.—D. A. Wocker.

PHYSIOLOGY

CARLSON, A. J.: *The physiology of aging*. (*North-west Med.*, V. 42, P. 6 and P. 46, 1943.)

Professor Carlson discusses the known processes of aging and points out that not all organs in the individual age in the same manner or at the same rate. In dealing with the digestive system he observes that while gall-stones become more common with increasing age, the function of the gall-bladder, if not diseased, remains relatively unimpaired. With increasing age the liver becomes more susceptible to various forms of injury. The secretion of pancreatic juice is not decreased. With advancing age the incidence of achlorhydria is increased (from about 5 per cent at age 20 to about 35 per cent at age (60) but the ability to secrete pepsin is not reduced.—F. X. Chockley.

METABOLISM AND NUTRITION

COLEMAN, J. V.: *Depression masked as malnutrition*. (*Psychiat. Quant.*, v. 18, p. 233, 1944).

There is a group of cases with depressive personalities in which rapid loss of weight, simulating an organic wasting disease, occupies the foreground of clinical interest. Psychological mechanisms of the weight loss are given.—Courtesy Psychosomatic Medicine.

LEVERTON, R. M., AND BRINKLEY, E. S.: *The copper metabolism and requirements of young women*. (*J. Nutrit.*, v. 27, p. 43, Jan., 1944).

A long-time study was performed on four young women on an adequate diet. Controls consisted of 95 studies, each of one week's duration, on 65 women maintained on their own self-chosen diet. The average daily intake of copper of the women on the self-chosen diet was 2.65 milligrams and average daily intake and retention were 2.14 and 0.23 milligrams respectively. As the copper intake increased, a larger proportion of each increase was retained. Evidence was obtained that the body does not excrete copper but that it is handled by the intestinal tract in a manner similar to iron.—I. M. Theone.

MCCANCE, R. A., AND WIDDOWSON, E. M.: *Seasonal and annual changes in the calcium metabolism in man*. (*J. Physiol.*, v. 102, p. 42, June, 1943).

In three out of six people studied, the authors found large seasonal variations in calcium absorption. Most calcium was absorbed in July and August, least in February and March. These changes were accompanied by corresponding changes in the urinary excretion of calcium. Administration of vitamin D was without influence on the calcium absorption during the period of least absorption. The absorption and excretion of magnesium showed no fluctuations with season.—M. H. F. Friedman.

ARIF, I., REKERS, P. E., PACK, G. T. AND RHODES, C. P.: *Metabolic studies in patients with cancer of the gastro-intestinal tract. X. Hypoproteinemia and anemia in patients with gastric cancer*. (*Ann. Surg.*, V. 118, P. 366, Sept. 1943.)

This work is based on the theory that the emaciation in gastric cancer could be due to impaired protein synthesis, which depends on the available amount of protein and its metabolism. If impaired, hypoproteinemia and anemia (disturbed hemoglobin synthesis) would result.

In comparison with 25 normal adults, 97 patients with gastric cancer showed hypoproteinemia (59%), and anemia (73%); 79% of the patients had an inadequate diet. The normal adults had no hypoproteinemia and only 4% had anemia.

Of the 97 patients, 20 were on an adequate diet (with 60% hypoproteinemia and 85% anemia) and the remaining 77 were on an inadequate diet (with 61% and 68% respectively). Dietary deficiency then could be eliminated as a cause.

Factors of age, economic status, and dietary background were eliminated by using 23 patients with non-neoplastic gastric disorders, and 21 with oral leukoplakia who had similar backgrounds. Thirty-five per cent of the first group and none of the second group had hypoproteinemia; 22% of the first group and 7% of the second group had anemia. Thus these factors were not responsible for the variation from normal. Continued blood loss could cause these two conditions. But of the 39 with chronic blood loss, 59% had hypoproteinemia and 72% were anemic, while 47 without chronic blood loss showed 67% and 74% respectively.

To determine if the presence of the tumor was a factor, studies were made on 12 patients who had had resections for gastric cancer. None were hypoproteinemic, though 25% were still anemic.

The cause of the anemia is not known; bleeding can not be responsible; and long continued administration of large amounts of ferrous salts or liver concentrates do not significantly alter the blood picture. But as it co-exists with the hypoproteinemia, it may also be due to impaired protein metabolism.—Ivan F. Bennett.

BIRGER, E. S.: *Daily vitamin C requirement in young children*. (*Pediatrics*, 1, p. 14, 1943).

Thirty-five children one year old and less were tested. Blood saturation with ascorbic acid was achieved by giving 35 milligrams of vitamin C a day in addition to that contained in the regular infant diet (3.5-6.5 milligrams per kilogram of weight).—Biological Abstracts.

QUASTEL, J. H.: *Enzymes and their mode of action*. (*Wallerstein Lab. Commun.* 6:182, 1943.)

A review was presented of the nature of enzymes and their actions. A general feature of the reversible enzymic action was its restriction to a particular type of molecular structure in the substrate. The kinetics of enzymic change were briefly presented. Initially the enzyme combined with the substrate to form an intermediate compound. A similar action was noted in which substances possessing attachment groupings related to those of the substrate combined reversibly with the enzyme and inhibited the specific action of the enzyme on the substrate. The role of prosthetic

groups consisting of organic metal complexes and of coenzymes acting as catalysts to the enzymic reaction was described, and the kinetics of cell metabolism were illustrated by the known enzymic relations existing in alcoholic fermentation.—Courtesy Biological Abstracts.

MISCELLANEOUS

MACHLE, W., HEYROTH, F. E., AND WITHERUP, S.: *The fate of methylcellulose in the human digestive tract.* (*J. Biol. Chem.*, v. 153, p. 551, 1944).

Either five or ten grams of methylcellulose were ingested by three human subjects. In ten experiments from 56.6 to 90.8 per cent of the methylcellulose taken was recovered from the feces. As the dietary roughage increased the amount of unaltered methylcellulose recovered in the feces decreased but the unrecovered portion was made up in approximately equivalent amounts of methoxyl groups. The excretion of methanol or formic acid by the kidney was not increased.—G. Klenner.

KORTUEM, C. M.: *Saliva glucose: A quantitative method for its determination in young children.* (*Tech. Bull. Registry Med. Tech.*, v. 5, p. 70, July, 1944).

The technique presented was employed on the saliva of 31 healthy infants from 15 to 40 months in age. In principle it is a modification of the micro method for quantitative determination of blood sugar of Folin and Folin and Malmios. 0.3 per cent sodium cyanide is added to the precipitating solution to clear and stabilize the supernatant fluid.

Results showed that, after ingestion of dextrose, the curve in 30 healthy infants rose from the fasting level of 10.6 mg to 51.8 mg of glucose per 100 cc. saliva at the end of 60 minutes, and 15 minutes later, fell to 21.3 mg per cent.—R. L. Burdick.

GAUDRY, R.: *Simplified spectrophotometric method for the determination of the concentration of alcohol in the blood* (*Rev. Canadienne Biol.*, v. 3, p. 328, July, 1944).

Measurement of the increase in color of chromium sulfate resulting from reduction of potassium dichromate by alcohol is made by means of a spectrophotometer. No standard solutions are required in the procedure. The degree of accuracy is well within clinical and medico-legal requirements. Determinations are made on 2 cc. samples of oxalated blood.—M. H. F. Friedman.

FANCHER, O. E., CALANDRA, J. C., AND FOSDICK, L. L.: *The effect of vitamins on acid formation in saliva.* (*J. Dental Res.*, v. 23, p. 23, Feb., 1944).

Following up reports that certain vitamins influence the activity of caries, the authors determined the influence of vitamins on acid formation in saliva. Saliva

was gathered by chewing paraffin and divided into portions, one portion of which served as a control. The control of fresh saliva was tested for calcium, incubated with the other portions and after incubation, was again tested for calcium. To the other portions were added glucose, powdered human tooth enamel and the test material. These samples were incubated for 4 hours with constant agitation.

The results showed that only vitamin K caused complete inhibition of acid formation in a 1.3 mg per 100 cc. concentration. There was some evidence that nicotinic acid, thiamin, "Cerophyl" and cholesterol may stimulate acid formation slightly.

These experiments were done on healthy, though caries-active, dental students who had an adequate diet. Therefore, it may be assumed that the vitamins were present in their saliva in optimum amounts and no attempt was made to remove these vitamins.—R. L. Burdick.

ROSE, J. A.: *Eating inhibitions in children in relation to anorexia nervosa.* (*Psychosom. Med.*, v. 5, p. 117, 1943).

Since suppression, or control of eating is the most impressive characteristic of anorexia nervosa, a study was made of cases in order to determine the general dynamics of the disorder. The study was enlarged to include anorexia of the very young since many authors place the onset of the disorder in the early years of life. Cases were selected from 10 years of child guidance clinic records, a college mental hygiene service, and a hospital teaching service. The special form of anorexia called anorexia nervosa, and seen as an entity when specific oral impregnation fears are found, is yet only a part of a large group of related anorexias. The fundamental problem of a psychological anorexia may be the same from birth; that is, that taking food either actually or symbolically means giving up the old and taking on new forms of psychobiological integration. The parental relationship plays a dominant role and, for this reason, early cases are best handled in a child guidance clinic where parents can be seen along with the child. Cases of anorexia in children who have parents seem to fall into 3 general categories. In the 1st group are frank or poorly concealed rejections. The children show many of the same difficulties that institutional children show. Another large group of cases is characterized by a close connection between the parent and child but where parental fear of mild degree is manifested to the child, either as forceful aggression or doubt. As might be expected the most severe difficulties involving feeding occur in children whose parents are deeply neurotic themselves. After adolescence, the majority of cases of severe anorexia occur in females. If the central core of the problem is resistance and fear of change, then the treatment experience should support the impetus to change in the present and allow the individual to overcome his present resistance; it is believed that it is impossible to make up to a patient therapeutically what the parent was unable to give.—Courtesy Biological Abstracts.

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